June 13, 2022

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Re: Toxicological Review of Formaldehyde Inhalation Toxicity; Draft Toxicological Review of Formaldehyde in Support of Summary Information on the Integrated Risk Information System; Notice of Availability and Request for Comment, 87 Fed. Reg. 72 (Apr. 14, 2022), Docket ID No. EPA-HQ-ORD-2010-0396

Dear Dr. Cascio,

The American Chemistry Council[1] ("ACC") Formaldehyde Panel[2] ("the Panel") appreciates the opportunity to provide comments on the Environmental Protection Agency's (EPA) 2022 Draft Integrated Risk Information System (IRIS) Toxicological Review of Formaldehyde-Inhalation (2022 Draft Assessment)[3].

EPA announced the availability of the 2022 Draft Assessment for public comment in a Federal Register[4] Notice (87 FR 22208) on April 14, 2022. The 60-day public comment period ends June 13, 2022, in advance of an external peer review by the National Academy of Sciences, Engineering, and Medicine (NASEM).

The 2022 Draft Assessment consists of four documents: main text (789 pages); supplemental information (1058 pages); assessment overview (193 pages), and draft charge questions (8 pages). While not documenting changes made based on interagency science consultation, the Agency also released a separate main text (780 pages), supplemental information (1063 pages) and assessment overview (191 pages) from the interagency process as well as more than 50 pages of comments from six agencies.

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[1] The American Chemistry Council (ACC) represents the leading companies engaged in the business of chemistry.
[2] The ACC Formaldehyde Panel represents producers, suppliers and users of formaldehyde and formaldehyde products, as well as trade associations representing key formaldehyde applications.
[3] https://ordspub.epa.gov/ords/eims/eimscomm.getfile?p_download_id=544587
[4] Federal Register :: Availability of the Draft IRIS Toxicological Review of Formaldehyde (Inhalation)

These comments outline substantive scientific and procedural flaws that persist from the previous Assessment including:

- EPA failed to adhere to EPA policy and procedural requirements in developing the 2022 Draft Assessment.
- The 2022 Draft Assessment does not fully incorporate NRC (2011) systematic review recommendations or current best practices for implementing systematic review in chemical toxicity assessments.
- The 2022 Draft Formaldehyde IRIS Assessment does not adhere to the 2020 Draft IRIS Handbook.
- The 2022 Draft Assessment conclusions are speculative and lack scientific confidence because of the application of a flawed and subjective study evaluation method, especially in the analysis and interpretation of the epidemiology data.
- Key studies were either dismissed, not considered, or only considered superficially in the 2022 Draft Assessment.
- The 2022 Draft Assessment fails to rely on the best available science, incorporate a weight-of-evidence approach or properly integrate evidence streams in assessing non-cancer and cancer endpoints.

Formaldehyde has a unique and robust dose-response and hazard assessment database that includes decades of published and peer reviewed literature on the differences and role of exogenous and endogenous formaldehyde in the generation of adverse health effects, lack of systemic distribution of inhaled formaldehyde, pharmacokinetic modeling, biological plausibility for adverse effects, non-linear threshold dose response, and dose-dependent transitions for endogenous compounds. The experimental evidence demonstrates that inhaled formaldehyde does not move beyond the portal-of-entry, there is a threshold for nasal tumor formation, and the published data (mechanistic, epidemiological, and toxicological) demonstrate a lack of biological plausibility for a causal association between inhaled formaldehyde and lymphohematopoietic cancers.

The Panel appreciates EPA's consideration of our comments. If you have any questions, please contact Lynn Dekleva at (202) 249-6704 or Lynn_Dekleva@americanchemistry.com.

Respectfully,

Lynn Dekleva PhD
Senior Director
Chemical Products & Technology Division
On behalf of the ACC Formaldehyde Panel

Executive Summary

The American Chemistry Council (ACC)[1] Formaldehyde Panel[2] (Panel) appreciates the opportunity to comment on EPA's 2022 Draft Toxicological Review of Formaldehyde – Inhalation[3] (2022 Draft Assessment).

An ad hoc committee of the National Academies of Sciences, Engineering and Medicine (NASEM) critically reviewed the 2010 Draft Assessment, the predecessor to the current draft. The NASEM 2011 review included scores of substantive recommendations to dramatically improve the 2010 Draft Assessment. For over a decade, EPA has been developing a new version of the assessment, prompted by the issuance of the NASESM 2011 report. The result is a massive document exceeding 2000 pages.

According to EPA, the 2022 Draft Assessment showcases a more systematic and transparent process than the 2010 Draft Assessment, which might suggest that the 2022 Draft Assessment represents an objective assessment of the best available science, especially of the science developed over the last decade in response to the NASEM 2011 report. But, as discussed extensively in Part 1 of the Panel's comments, the 2022 Draft Assessment reflects many of the scientific flaws that NASEM criticized in the earlier draft. Equally problematic, in developing the 2022 Draft Assessment, EPA inexplicably failed to comport with numerous policy and procedural requirement that compounded the scientific flaws.

Key issues discussed in Part 1 and Part 2 of the Panel's comment include the following:

Part 1

Systematic Review

- The 2022 Draft Assessment does not fully incorporate NASEM's (2011) systematic review recommendations or current best practices for implementing systematic review.
- Scores of key studies were either dismissed, not considered, or only considered superficially in the 2022 Draft Assessment (see Appendix A of the Panel's comments). This seriously calls into question the completeness of EPA's systematic review process and if the 2022 Draft Assessment represents the best available science.
- The 2022 Draft Assessment fails to incorporate a weight of evidence approach or properly integrate evidence streams in assessing non-cancer and cancer endpoints.

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[2] The ACC Formaldehyde Panel represents producers, suppliers and users of formaldehyde and formaldehyde products, as well as trade associations representing key formaldehyde applications.

[3] https://ordspub.epa.gov/ords/eims/eimscomm.getfile?p_download_id=544587

Endogenous Formaldehyde Exposure

- The 2022 Draft Assessment does not consider how exogenous formaldehyde exposure appreciably alters normal endogenous formaldehyde concentrations to produce portal of entry or systemic effects as recommended by the NASEM review (NASEM 2011).
- Toxicokinetics was not integrated into the hazard classification or dose response assessments and EPA omitted key evidence demonstrating no systemic distribution of inhaled formaldehyde.

Systemic Effects

Myeloid Leukemia

- For myeloid leukemia, the 2022 Draft Assessment continues to rely on largely null epidemiological evidence, weak animal evidence, and no established biologically plausible MOA, all of which were identified as issues by the NASEM review (NASEM 2011).
- The best available science does not support a causal association between formaldehyde and myeloid leukemia; therefore EPA's derived IUR is wholly inappropriate.
- The Draft Assessment hypothesizes a mode of action "network" that is not supported by the experimental evidence and does not advance biological plausibility.
- The Draft Assessment groups AML (Acute Myeloid Leukemia) and CML (Chronic Myeloid Leukemia) together, contrary to 2011 NRC recommendations.
- The epidemiological evidence does not support an association between formaldehyde exposures (duration of exposure, average intensity or TWA (Time Weighted Average) exposure, cumulative exposure, or peak exposure) and myeloid leukemia, acute myeloid leukemia, or chronic myeloid leukemia. This lack of any discernible pattern with exposure metric suggests that the reported associations are likely due to chance.

Noncancer Health Endpoints: Systemic Effects

- The best available science does not support EPA's findings of a connection between formaldehyde and reproductive and developmental effects.
- The best available science is not "suggestive evidence" of nervous system effects from formaldehyde.

Portal of Entry Effects

NPC

- The 2022 Draft Assessment repeatedly cites its Cancer Guidelines but fails to properly apply them. As a result, EPA's Draft Assessment develops a linear unit risk estimate for NPC that is essentially unchanged from the value derived over 30 years ago, despite the prodigious growth in the scientific database on formaldehyde indicating that formaldehyde is a threshold carcinogen.

- The 2022 Draft Assessment misinterpreted the work of Dr. Marsh and failed to identify the work of Thompson et al. (2020), which provides important data integration related to the MOA for formaldehyde-induced nasal tumors.
- Evidence demonstrates that formaldehyde does not induce NPC through a genotoxic mechanism; instead, NPC is secondary to cytotoxicity and cell proliferation.
- Evidence also demonstrates that formaldehyde is not a genotoxic carcinogen.

Noncancer Health Endpoints

- The 2022 Draft Assessment does not apply a weight of evidence approach in assessing sensory irritation.
- The 2022 Draft Assessment inappropriately dismisses carefully designed chamber studies, disregarding the 2011 NASEM recommendation, and relies on subjective measures of adverse effects in uncontrolled studies.
- The 2022 Draft Assessment uses subjective measures of adverse effects for developing noncancer RfCs.
- EPA's weight of evidence conclusions regarding inhalation of formaldehyde and asthma are not scientifically justified and not based on the best available science.

Biologically-based dose response modeling (BBDR).

- EPA's approach to the evaluation of BBDR Modeling in the 2022 Draft Assessment was focused on discounting the model, rather than working to refine it, which is inconsistent with EPA's 2005 Cancer Guidelines.

Part 2

EPA impermissibly deviated from key steps in its established IRIS process.

- In developing the 2022 Draft Assessment, EPA failed to fully implement step 1 of the IRIS process - EPA never released an IRIS assessment plan, which would have included scoping and problem formulation materials.
- Interagency science consultation process for EPA's 2022 Draft Assessment undermines transparency and did not elicit information from potentially impacted federal agencies.

As a significant guidance document, the 2022 Draft Assessment should have been subject to interagency review under E.O. 12866.

The 2022 Draft Assessment failed to adhere to proper peer review processes.

- The NASEM Responsible Staff Officer tasked with managing the peer review of the 2022 Draft Assessment was previously an EPA career scientist within the IRIS Program. During that time, she was actively engaged in developing and reviewing earlier drafts of the formaldehyde assessment.
- The Responsible Staff Officer actively solicited names of potential committee members from the same EPA employees with whom she had previously worked and from the same Agency that is funding the peer review of the 2022 Draft Assessment.

EPA's Approach to public comment and the scope of the peer review is inconsistent with Agency policy and legal requirements for regulatory action.

- EPA has not sought meaningful comment on draft charge questions and peer review committee tasks. Additionally, EPA and NASEM's sequencing of public comment, 2022 Draft Assessment revisions, and selection of peer reviewers undermines the rigor of the peer review.

EPA inappropriately failed to fully document incorporation of the NASEM 2011 Recommendations on the 2010 Draft Assessment.

EPA has failed to follow Agency and OMB requirements to reduce the misuse, including in final agency regulatory actions, of the 2022 Draft Assessment.

- EPA's *Peer Review Handbook* states that draft work products, prior to peer review or subsequent revisions, are inappropriate for regulatory decisions.

The Panel urges EPA to substantially revise the 2022 Draft Assessment to accurately convey the best available science in a weight of evidence approach as discussed in Part 1 of these comments. EPA should reset its 2022 Draft Assessment review process and conduct it in a manner that fully addresses the concerns raised in Part 2 of the Panel's comments.

In light of the forthcoming NASEM peer review of the 2022 Draft Assessment, the Panel reserves the right to supplement these comments. In addition, the Panel endorses and incorporates herein by reference the comments submitted under separate cover by the American Chemistry Council, including the Formaldehyde Risk Evaluation Consortium; ACC member companies and the comments submitted by the many scientists who submitted comments on the 2022 Draft Assessment, and which are referenced throughout the Panel's comments.

I. EPA Failed to Adhere to EPA Policy, Procedural and Legal Requirements in Developing the 2022 Draft Assessment

A. The 2022 Draft Assessment is subject to EPA's Information Quality Guidelines

Congress enacted the Information Quality Act (IQA),[4] "to ensur[e] the quality, objectivity, utility, and integrity of information …disseminated by Federal agencies" such as EPA. The IQA mandated the Office of Management and Budget (OMB) to issue government-wide guidance, which each federal agency was to follow in issuing their own guidelines. In February 2002, OMB issued its guidelines; later that same year, EPA issued its agency-specific guidelines (EPA IQA Guidelines). The EPA IQA Guidelines apply the OMB Guidelines to EPA's particular circumstances and "establish administrative mechanisms allowing affected persons to seek and obtain correction of information …disseminated by the agency that does not comply with the OMB or agency guidelines…."[5]

EPA's 2022 Toxicological Review of Formaldehyde – Inhalation, (2022 Draft Assessment) must adhere to a rigorous standard of quality because it is "influential" information as set forth in EPA's IQA Guidelines. In particular, the 2022 Draft Assessment will (1) "have a clear and substantial impact on important public policies or private sector decisions" and involve "controversial scientific […] issues," and (2) be a major work product that is poised to undergo peer review by an ad hoc committee of the National Academies of Sciences, Engineering, and Medicine (NASEM).[6]

Ensuring and maximizing the quality of the 2022 Draft Assessment requires the application of "a 'weight-of-evidence' approach that considers all relevant information and its quality […]."[7] Equally important, the substance of the information must be "accurate, reliable and unbiased," which entails the use of "the best available science and supporting studies conducted in accordance with sound and objective scientific practices […]."[8] EPA must ensure that the information presented in the 2022 Draft Assessment "is comprehensive, informative, and understandable."[9]

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[4] Pub. L. No. 106-554, 114 Stat. 2763A-153 to 2763A-154.

[5] U.S. ENVIRONMENTAL PROTECTION AGENCY. 2022. Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the Environmental Protection Agency. Accessed online at: https://www.epa.gov/sites/default/files/2015-07/documents/epa_infoqualityguidelines.pdf [hereinafter EPA's IQA Guidelines]

[6] EPA's IQA Guidelines at 20.

[7] EPA's IQA Guidelines at 21.

[8] The definition of best available science mirrors the language of the decision in Chlorine Chemistry Council v. EPA, 206 F.3d 1286 (D.C. Cir. 2000).

[9] EPA's IQA Guidelines

B. Even in the absence of EPA's Information Quality Guidelines, TSCA sets forth scientific standards

TSCA sets forth scientific standards that apply to any scientific document relied upon by EPA, including a final formaldehyde assessment, in risk evaluations under TSCA section 6.[10] In particular, TSCA mandates the use of the "best available science," which is subject to a "weight of scientific evidence" approach. Properly weighing the scientific evidence necessarily entails employing a systematic review method.[11] Thus, before EPA can use any final IRIS assessment for any TSCA section 6 risk evaluation, EPA must ensure that the final IRIS assessment comports with TSCA's section 26 standards.

TSCA section 26 standards also require EPA to consider, among other factors, "the extent to which the variability and uncertainty… are evaluated and characterized" and "the extent of independent verification or peer review of the information or of the procedures, measures, methods, protocols, methodologies, or models."[12] Therefore, before EPA relies on a final formaldehyde assessment for TSCA purposes, it must fully address the anticipated NASEM recommendations from its upcoming review of the 2022 Draft Assessment, and the prior 2011 NASEM recommendations from the 2010 Draft Assessment.

C. The 2022 Draft Assessment must comply with EPA's Guidelines for Carcinogenic Risk Assessment

In implementing its Information Guidelines, EPA relies on existing guidelines and policies,[13] which includes EPA's Guidelines for Carcinogenic Risk Assessment (Cancer Guidelines).[14] The Cancer Guidelines explicitly note that "when judging and considering the use of any data, the basic standard of quality, as defined by the EPA Information Quality Guidelines, should be satisfied."[15]

EPA's Cancer Guidelines emphasize "a critical analysis of all the available information that is relevant to assessing the carcinogenic risk," rather than reliance on default options as the starting point.[16] A nonlinear approach should be utilized when, as in the case of formaldehyde, "there

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[10] 15 U.S.C. §2605

[11] 82 FR 33748, available at https://www.govinfo.gov/content/pkg/FR-2017-07-20/pdf/2017-14337.pdf ("Weight of scientific evidence means a **systematic review method**, applied in a manner suited to the nature of the evidence or decision, that **uses a pre-established protocol** to comprehensively, objectively, **transparently, and consistently**, identify and evaluate each stream of evidence, including strengths, limitations, and relevance of **each study** and to integrate evidence as necessary and appropriate based upon strengths, limitations, and relevance.)

[12] 15 U.S. Code § 2625(h).

[13] EPA. (2005). Guidelines for Carcinogen Risk Assessment. Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC, EPA/630/P-03/001F at 10 [hereinafter Cancer Guidelines] ("EPA intends to implement these Guidelines […] in a harmonious way in conjunction with our existing guidelines and policies […].")

[14] Cancer Guidelines

[15] Cancer Guidelines at 2-36

[16] Cancer Guidelines

are sufficient data to ascertain the mode of action and conclude that it is not linear at low doses and the agent does not demonstrate mutagenic or other activity consistent with linearity at low doses."[17] The Cancer Guidelines also stress the importance of relying upon, "common sense reasonable applications of assumptions and policy, and transparency…to avoid unrealistically high [risk] estimates."[18]

D. EPA's Information Quality Guidelines also extend to EPA's standard IRIS Procedures.

In the 2022 Draft Assessment, EPA relied in part on "standard IRIS Procedures" as described in the ORD Staff Handbook for Developing IRIS Assessments (IRIS Handbook). The IRIS Handbook, however, in its current form, contains the following disclaimer:

> This document is distributed solely for the purpose of pre-dissemination public comment under applicable information quality guidelines. It has not been formally disseminated by the U.S. Environmental Protection Agency. It does not represent and should not be construed to represent any agency determination or policy.[19]

We find this disclaimer puzzling given that EPA did in fact use the "standard IRIS procedures" as described in the IRIS Handbook in developing the 2022 Draft Assessment. Thus, EPA's use of the information in the IRIS Handbook, and, therefore, its "dissemination," triggers the application of the EPA Information Quality Guidelines.

As discussed below, however, EPA did not ensure and maximize the quality of the IRIS Handbook *before* using it to develop the 2022 Draft Assessment. The deficiencies within the IRIS Handbook further compound the deficiencies in the 2022 Draft Assessment. In particular, EPA neither references nor integrates into the 2022 Draft Assessment dozens of studies, which are listed in Appendix A, and discussed throughout these comments. In its review of the 2010 Draft Assessment, NASEM raised a similar issue. In the context of asthma pathogenesis, NASEM noted that: "Abundant research and review articles are available and should have been cited…."[20]

Thus, the 2022 Draft Assessment fails to rely on the best available science and apply a transparent and systematic review incorporating a weight-of-evidence approach that properly integrates evidence streams in assessing potential non-cancer and cancer risks of formaldehyde exposures, especially at human relevant, low levels of exposure. Moreover, EPA repeatedly cites its Cancer Guidelines but fails to properly apply them. As a result, EPA's linear unit risk estimate for NPC is essentially unchanged from the value derived over 30 years ago, despite the

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[17] Cancer Guidelines at 3-22.
[18] Cancer Guidelines at 5-2
[19] US EPA. 2020. ORD Staff Handbook for Developing IRIS Assessments (Public Comment Draft, Nov 2020). U.S. EPA Office of Research and Development, Washington, DC, EPA/600/R-20/137, 2020. Accessed online at: https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=350086 [hereinafter IRIS Handbook].
[20] NASEM 2011 at 80.

prodigious growth in the scientific database on formaldehyde indicating that formaldehyde is a threshold carcinogen.

Unless the substantive deficiencies of the 2022 Draft Assessment are fully addressed and reconciled with the rigorous EPA Information Quality Guidelines and Cancer Guidelines the assessment cannot be disseminated and relied upon by any federal agency.

II. Systematic Review: EPA did not ensure and maximize the quality of the IRIS Handbook *before* using it to develop the 2022 Draft Assessment

A. The 2022 Draft Assessment does not fully incorporate NASEM (2011) systematic review recommendations or current best practices for implementing systematic review in chemical toxicity assessments.

Until recently, the IRIS program did not have published guidance for the methodology employed in its toxicological assessments. The lack of a standardized procedure led to inconsistency across assessments conducted by different EPA chemical managers, contractors, and other EPA staff. Many of the assessments published in the years leading up to 2011 were received critically by some stakeholders.

EPA asked the National Research Council (NRC, now NASEM) to conduct an independent scientific review of the 2010 draft formaldehyde assessment, which was released in 2011.[21] The NASEM review was critical not only of the formaldehyde assessment but also the IRIS process in general; the Committee recommended broad changes to increase consistency, objectivity, and transparency in IRIS assessments. The general findings of NASEM were summarized as follows:

> In general, the committee found that the draft was not prepared in a consistent fashion; it lacks clear links to an underlying conceptual framework; and it does not contain sufficient documentation on methods and criteria for identifying evidence from epidemiologic and experimental studies, for critically evaluating individual studies, for assessing the weight of evidence, and for selecting studies for derivation of the RfCs [reference concentrations] and unit risk estimates.[22]

In the years following the NASEM 2011 review, NASEM recommended that EPA develop a handbook to guide IRIS assessments and incorporate principles of systematic review into the IRIS process. Systematic review approaches facilitate objective, transparent, and reproducible methods to retrieve, organize, evaluate, integrate, and communicate the results of chemical risk

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[21] NRC (National Research Council). 2011. Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde. Washington, DC: The National Academies Press. https://doi.org/10.17226/13142 [hereinafter NASEM 2011].

[22] NASEM 2011 at 4.

assessments.[23] The IRIS Handbook was released in November 2020 for public comment and review by NASEM.

Given the many substantive recommendations by the NASEM committee (2011), EPA decided to develop a new formaldehyde assessment "from scratch." The April 2022 Draft of the Toxicological Review of Formaldehyde-Inhalation for the IRIS program (2022 Draft Assessment[24]) indicates that it is a "newly developed" assessment that addresses comments from the prior NASEM Panel on the 2010 IRIS Formaldehyde Draft Assessment (2010 Draft Assessment). According to the methods described in the 2022 Draft Assessment, EPA initiated a new formaldehyde assessment in 2012, conducting literature searches until the draft was suspended in 2017; it was subsequently "unsuspended" in March 2021.

The 2022 Draft Assessment was thus in development during the steady and substantive evolution of the systematic review process in chemical risk assessment over the last decade. Consequently, the **2022 Draft Assessment does not reflect the best practices for systematic review.** In the sections that follow, examples are provided for each of the major phases of the systematic review process.

1.0 The 2022 Draft Assessment does not discuss scoping or problem formulation activities for the "newly developed" assessment.

The 2011 NASEM committee recommended that EPA develop the scope of IRIS reviews around biological plausibility and mode of action (MOA) information, recommending that EPA "select outcomes [for assessment] on the basis of available evidence and understanding of mode of action" and to consider whether the scientific evidence indicated that a hypothesized exposure-disease association was biologically plausible.[25] Perhaps because this particular NASEM recommendation was generic to systematic review and not formaldehyde *per se*, EPA has not provided a response to it in Appendix D of the 2022 Draft Assessment.[26]

Since the NASEM (2011) review, agencies and authorities on systematic review have consistently stated that transparent and thoughtful scoping and problem formulation is a key

[23] IRIS Handbook at xiii.
[24] U.S. EPA. IRIS Toxicological Review of Formaldehyde-Inhalation (External Review Draft, 2022). U.S. Environmental Protection Agency, Washington, DC, EPA/635/R-22/039, 2022.
[25] NASEM 2011 at 164.
[26] US EPA. 2022. Toxicological Review of Formaldehyde-Inhalation, Supplemental Information (External Review Draft). Washington, DC. Accessed online at https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=248150 [hereinafter 2022 Draft Assessment].

component of a well-designed systematic review.[27,28,29,30] For example, the World Health Organization (WHO) systematic review framework states:

> A rigorous, well planned problem formulation process is a major factor in ensuring that an assessment project yields a successful result…It is recommended that problem formulation is carried out by a multidisciplinary team also involving risk managers to ensure that the scope of the review addresses management needs.[31]

Critically, WHO also emphasizes:

> "Because **it may not be necessary or feasible to conduct a systematic review for every health outcome** or every exposure scenario in a chemical risk assessment – particularly for a data-rich chemical – the problem formulation process will often involve both identification and prioritization of topics"[32]

Consistent with the recommendations from the NASEM (2011) review of the 2010 Draft Assessment, EPA should have engaged in an explicit scoping and problem formulation process to specifically address best available evidence-based health outcomes in the context of mode of action.

1.1 The 2022 Draft Assessment does not respond to NASEM's recommendation to clearly document its methods for study selection.

As noted above, NASEM criticized the 2010 Draft Assessment for not providing a clear method for identifying and evaluating individual studies. NASEM (2011) specifically requested an "a priori presentation of the study selection criteria."[33] While a generic framework was provided, the 2022 Draft Assessment does not clearly describe or document study selection, particularly for studies publishing between 2017 and 2021.

As noted, systematic review methods have developed substantively since the NASEM 2011 review. The IRIS Handbook includes a highly detailed and structured process for literature

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[27] NTP (National Toxicology Program). 2019. Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. March 4, 2019. Research Triangle Park, NC Office of Health Assessment and Translation (OHAT), Division of the National Toxicology Program, National Institute of Environmental Health Sciences.

[28] EFSA (European Food Safety Authority). 2017. Scientific Opinion on the guidance on the use of the weight of evidence approach in scientific assessments. EFSA Journal 2017;15(8):4971, 69 pp. https://doi.org/10.2903/j.efsa.2017.4971

[29] EPA (United States Environmental Protection Agency). 2021. Draft Protocol for Systematic Review in TSCA Risk Evaluations. Office of Chemical Safety and Pollution Prevention, U.S. EPA, Washington, DC., EPA Document# EPA-D-20-031. Accessed online at https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/draft-protocol-systematic-review-tsca-risk-evaluations

[30] WHO (World Health Organization). 2021. Framework for the use of systematic review in chemical risk assessment. World Health Organization. https://apps.who.int/iris/handle/10665/347876. License: CC BY-NC-SA 3.0 [hereinafter WHO 2021].

[31] WHO 2021 at 16.

[32] WHO 2021 at 17.

[33] NASEM 2011 at 211.

search and selection. However, the process for inclusion and exclusion of studies from IRIS assessments, including formaldehyde, diverges from current best practices. For example, there are numerous places in the systematic review when EPA can choose to exclude studies without justification, including after refinement of the study plan or organization of the hazard assessment.

The 2022 Draft Assessment provides a broad generic Population (including animal species), Exposure, Comparator, and Outcomes (PECO) statement as well as outcome-specific inclusion and exclusion criteria provided in Appendix A.5 (developed in the initial 2012-2016 time period of the assessment prior to suspension). The initial 2012-2016 search and selection process discussed in Appendix A.5 generally follows typical systematic literature review methods with an important exception – some of the studies were excluded after the full-text review for PECO relevance, but the specific studies and reasoning are not documented. For example, for human studies of upper respiratory and lymphohematopoietic malignancies published through 2016, 59 articles were included through the initial title and abstract screen followed by the full-text screening; of these 59 studies, 47 were included and 12 were excluded for unknown reasons.

Appendix F details the process for literature published between 2016 and 2021. In brief, studies from this time period that met the PECO criteria were further reviewed to determine if **"they could potentially be impactful to the assessment with respect to changing hazard conclusions or toxicity values presented in the 2017 draft"** (emphasis added).[34] The criteria for determining whether the studies were "impactful" are vague and subjective, and thus EPA's process for reaching these decisions remains unclear. Perhaps most importantly, **determination of a new study's impact was clearly tied to previously drawn hazard conclusions in the 2017 draft**. As stated on page F-6 of the 2022 Draft Assessment, impactful studies included:

- More apical endpoints and those most directly related to the mechanistic uncertainties identified in the 2017 draft as most relevant to drawing hazard or dose-response judgments were considered more impactful. The specifics of this consideration vary depending on the health outcome(s) of interest. In some cases, this relevance determination relates to the potential human relevance of the endpoints, while in others this relates to an ability to infer adversity.[35]

But how was the process of determining which studies were "most relevant" conducted? For example, how is human relevance determined?

- For human studies, prioritization considerations depended on the health effect category, formaldehyde exposure levels, **and the extent of the evidence base supporting the hazard conclusions in the 2017 draft.** Studies of noncancer respiratory outcomes identified in the PECOs among residential populations or school-aged children were prioritized over occupational studies, which typically involve higher formaldehyde concentrations. Any study of reproductive or developmental outcomes that conducted an exposure assessment (qualitative or quantitative) for formaldehyde was considered possibly impactful. In addition, with some exceptions documented in the inventory

[34] 2022 Draft Assessment (Appendix) at F-5.
[35] 2022 Draft Assessment (Appendix) at F-6.

tables, studies of ALS, genotoxicity endpoints, or PECO identified cancer outcomes that conducted an exposure assessment (qualitative or quantitative) for formaldehyde were generally considered possibly impactful" (emphasis added).[36]

Does this imply that EPA excluded all studies reporting on previously unreported endpoints (which could plausibly include effects earlier in a causal pathway), or studies that did *not* support one of the hazards identified in the 2017 draft?

As an example of this unclear and apparently subjective process, Table F-5 provides the results of EPA's assessment of 2016-2021 publications pertaining to asthma. One of the studies deemed "not impactful" is a 2020 occupational cohort study conducted in the United States (Dumas, 2020). This study of physician-diagnosed asthma was purportedly excluded for the following reasons "occupational exposure – adults, **health effects well supported in assessment**" (emphasis added).[37]

However, Dumas (2020), a prospective cohort study, found no statistically significant associations between high-level exposure to formaldehyde (among other disinfectants) in nurses, as evaluated by a Job-Task-Exposure Matrix. Thus, contrary to the reasoning for its exclusion, this seemingly well conducted occupational exposure study did not support an association between formaldehyde and asthma, but was excluded, nonetheless.

1.2 The 2022 Draft Assessment does not incorporate best practice recommendations from NASEM and other agencies on the evaluation and integration of MOA information.

In its 2011 review, the NASEM Committee commented several times on EPA's use of information on potential modes of action (MOAs) for various health effects in the 2010 Draft Assessment. Broadly, NASEM stated:

> …the draft assessment presents discussions on mode of action that vary in level of detail, analysis and referencing. In some cases, mode-of-action data – which would support EPA's conclusions—are available, but they are not presented in the draft assessment. In those cases, the committee recommends that those data be reviewed and evaluated. **In other cases, mode of action is highly speculative**, and the speculations are discussed at length in the draft assessment. In those cases, the committee recommends that the discussion be truncated given the speculative nature of the hypotheses (emphasis added).[38]

Other systematic review frameworks recommend evaluating mechanistic information and information on potential MOAs with the same level of rigor as the other lines of evidence (animal and human). WHO (2021) is particularly clear on this matter, stating:

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[36] 2022 Draft Assessment (Appendix) at F-6.
[37] 2022 Draft Assessment (Appendix) at F-13.
[38] NASEM 2011 at 22.

> Regarding mechanistic and pharmacokinetic data (two separate types of data), these are often described as being contextual or associated with subquestions. **However, if these data are anticipated to be critical in making determinations of hazard or dose–response, such data should be included in the review and subjected to the same appraisal and structured evaluation process applied for other data types** (emphasis added).[39]

Indeed, as made clear in the NASEM (2011) comments and given the highly reactive nature of formaldehyde, MOA information is of critical importance for the interpretation of multiple potential cancer and non-cancer effects.

The 2022 Draft Assessment, however, does not appear to implement any of these best practices for the use of mechanistic studies and MOA information. Mechanistic studies and information supporting (or not supporting) MOA are largely relegated to "supplemental" information and considered only in the evidence integration phase in the context of their ability to inform hazard conclusions based on human and animal evidence.

The 2022 Draft Assessment does include more discussion of MOAs relative to the 2010 Draft Assessment. EPA acknowledges that inhaled formaldehyde is not distributed to an appreciable extent beyond the respiratory tract to distant sites. EPA, therefore, assumes inhaled formaldehyde acts via a different pathway. Although EPA looks at endpoints that could be key events in an MOA, EPA has not proposed a biologically plausible MOA.

Based on the current understanding of the toxicokinetics of formaldehyde inhalation exposure (see Appendix A.2), practical working assumptions were applied to this assessment. Although some uncertainties remain, the organization and analyses in the assessment assume that inhaled formaldehyde is not distributed to an appreciable extent beyond the respiratory tract to distal tissues; thus, it is assumed that inhaled formaldehyde acts via a pathway different from a direct interaction with tissues distal to the portal of entry (POE) to elicit observed systemic effects. Similarly, it is assumed that formaldehyde does not cause appreciable changes in normal metabolic processes associated with formaldehyde in distal tissues. Thus, studies examining potential associations between levels of formaldehyde or formaldehyde byproducts in tissues distal to the POE (e.g., formate in blood or urine, brain formaldehyde levels) and health outcomes are not considered relevant here to interpreting the human health hazards of inhaled formaldehyde.[40]

In fact, the postulated MOA is lacking any experimental data to support EPA's conclusion that inhaled formaldehyde that EPA acknowledges is not distributed to sites beyond the portal of entry and causes cancer.

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[39] WHO 2021 at 18.

[40] 2022 Draft Assessment at xxi.

1.3 The 2022 Draft Assessment's treatment of MOA and mechanistic data renders it inappropriate for regulatory use

EPA's dismissal of the importance of MOA and mechanistic information is inconsistent with the Agency's own approach to human health hazard assessment for a given chemical under the Toxic Substances Control Act (TSCA), one of the stated objectives for the 2022 Draft Assessment. [41] EPA's guidelines governing application of systematic review in TSCA risk evaluations characterizes the "the availability of a fully elucidated mode of action (MOA) or adverse outcome pathway (AOP)" as "highly preferred." These guidelines argue that "[m]echanistic evidence may provide support for biological plausibility and help explain differences in tissue sensitivity, species, gender, life-stage or other factors," emphasizing that "EPA/OPPT plans to prioritize the evaluation of mechanistic evidence instead of evaluating all of the identified evidence upfront. This approach has the advantage of conducting a focused review of those mechanistic studies that are most relevant to the hazards under evaluation."[42]

1.4 The 2022 Draft Assessment does not incorporate best practices for evidence synthesis.

The process of evidence synthesis (within lines of evidence) and evidence integration (across lines of evidence) are critical but still somewhat underdeveloped areas of systematic review. In the 2022 Draft Assessment, the procedure is described, but only in general terms, as depicted in the figure below (a figure that is found in the 2022 Draft Assessment but does not appear in the IRIS Handbook). Further, it is notable that there is no discussion of mechanistic studies or information on MOA.

[41] https://www.epa.gov/sites/default/files/2020-09/documents/casrn_50-00-0-formaldehyde_finalscope_cor.pdf (p. 74).
[42] https://www.epa.gov/sites/default/files/2018-06/documents/final_application_of_sr_in_tsca_05-31-18.pdf.

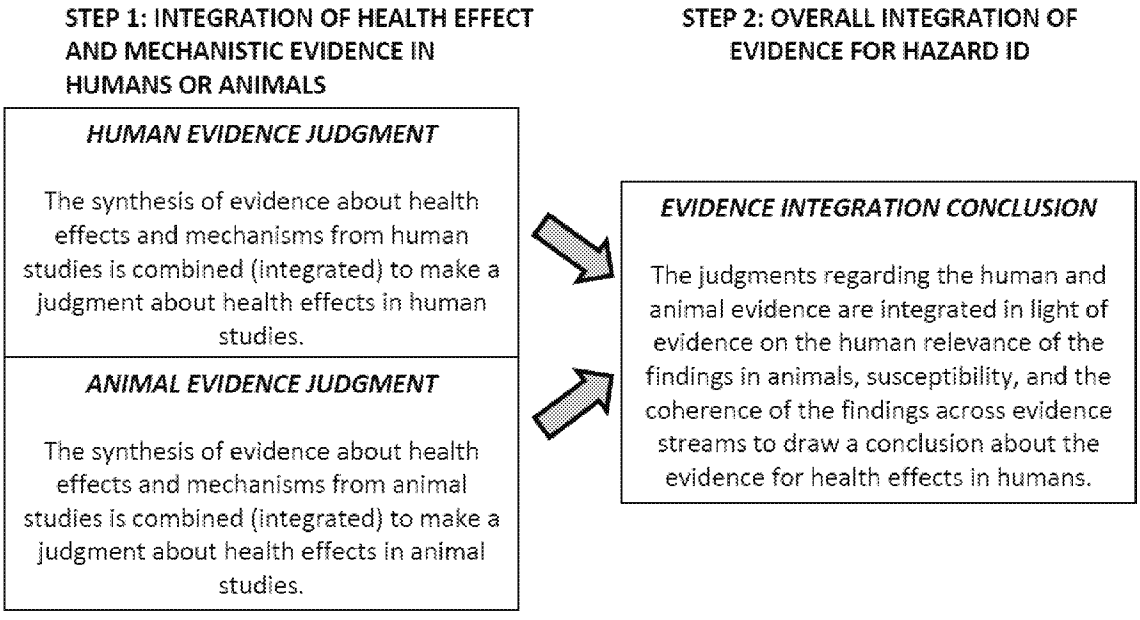

Figure III. Process for evidence integration.

Evidence synthesis is the phase of the review in which EPA integrates evidence within a line of inquiry (e.g., epidemiology, toxicology) to develop an "evidence judgment." An area of focus in the NASEM 2011 formaldehyde review was in EPA's synthesis of individual streams of evidence for specific endpoints (e.g., lymphohematopoietic cancers) when considering the "highly variable" epidemiologic literature and the uncertain mode of action. The 2011 NASEM noted that the differing features and findings of these studies would need to be discussed and weighed, "specifically as to how they were taken into account in EPA's determination of causality".[43] The review goes on to state:

> For example, in the highly influential National Cancer Institute (NCI) cohort study (Beane-Freeman et al. 2009), the strength and specificity of the exposure-response associations varied considerably over the period in which the cohort was followed. In addition, the reliance on the peak-exposure metric to determine causality in that study rather than the more conventional dose metric of cumulative exposure should be further justified, particularly in the absence of established modes of action.[44]

[43] NASEM 2011 at 111.
[44] NASEM 2011 at 111.

There are numerous guidance documents that detail similar recommendations as NASEM (2011) for synthesizing evidence (e.g., EFSA 2017;[45] NTP 2019[46]; WHO 2021[47]). The general process for evidence synthesis for the 2022 Draft Assessment, described in ES-2, is largely aligned with this guidance. The 2022 Draft Assessment methods section indicates that consistency, magnitude of effects, and dose-response gradients should be emphasized when considering epidemiological and controlled human exposure studies. With regard to consistency, EPA states that "Consistency between studies was examined by comparing study results by confidence level, specific methodological features that contributed to potential bias, exposure setting, and level of exposure." [48] Notably, Table III further describes:

> When inconsistencies exist, the synthesis considers whether results were "conflicting" (i.e., unexplained positive and negative results in similarly exposed human populations or in similar animal models) or "differing" (i.e., mixed results explained by differences between human populations, animal models, exposure conditions, or study methods) (U.S. EPA, 2005a) based on analyses of potentially important explanatory factors….[49]

However, the analysis in the 2022 Draft Assessment falls short of applying the systematic review principles outlined in the methods section. An example is the 2022 Draft Assessment's treatment of the existing epidemiological evidence on formaldehyde.

The 2022 Draft Assessment concludes that the human evidence for myeloid leukemia is "robust" based on "consistent increases in risk across a set of high and medium confidence… studies…strong associations…and…temporal relationship[s] consistent with causality."[50] However, setting aside the inappropriate grouping of acute myeloid leukemia (AML) and chronic myeloid leukemia (CML), the body of epidemiological evidence on myeloid leukemia does not provide "robust evidence" of an association – it is neither consistent nor strong. Specifically, epidemiological studies of occupational groups historically highly exposed to formaldehyde generally do not demonstrate statistically significantly increased rates of myeloid leukemia or more specifically AML and CML:

1. No statistically significant excess risk above background rates of myeloid leukemia is reported in the three myeloid leukemia studies rated as having "effect estimates classified

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[45] EFSA (European Food Safety Authority). 2017. Scientific Opinion on the guidance on the use of the weight of evidence approach in scientific assessments. EFSA Journal 2017;15(8):4971, 69 pp. https://doi.org/10.2903/j.efsa.2017.4971.

[46] NTP (National Toxicology Program). 2019. Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. March 4, 2019. Research Triangle Park, NC Office of Health Assessment and Translation (OHAT), Division of the National Toxicology Program, National Institute of Environmental Health Sciences.

[47] WHO. 2021.

[48] 2022 Draft Assessment at xxv.

[49] 2022 Draft Assessment at xxxv.

[50] 2022 Draft Assessment at 1-542.

with high confidence" (Hauptmann et al., 2009; Beane Freeman et al., 2009; Meyers et al. 2013).

2. Results from studies with as high or higher quality observed no significant increases in AML, CML, or myeloid leukemia (Saberi Hosnijeh et al. 2013, Talibov et al. 2014, Checkoway et al. 2015).
3. Results do not indicate consistent excesses across exposure measures in the studies rated "high confidence" (Hauptmann et al., 2009; Beane Freeman et al., 2009; Myers et al. 2013).

Overall, there is no "reasonable confidence that alternative explanations" (i.e., chance) can be ruled out.

1.5 The 2022 Draft Assessment does not incorporate best practices for evidence integration.

In 2011, NASEM gave the following recommendation (in this case, in regard to the lymphohematopoietic malignancies):

> As stated in EPA's cancer guidelines, EPA's approach to weight of evidence should include "a single integrative step after assessing all of the individual lines of evidence."[51] Although a synthesis and summary are provided, the process that EPA used to weigh different lines of evidence and how that evidence was integrated into a final conclusion are not apparent in the draft assessment and should be made clear in the final version.

EPA's Cancer Guidelines also state:

> For both noncancer health effects and carcinogenicity, it is important to transparently and succinctly convey the evidence integration judgments, the supporting rationale, and the key data supporting those decisions.... Throughout this expert judgment-driven decision process, there can be instances where it may make sense to lay out both sides of a controversial argument (as well as the implications of each) before drawing evidence integration conclusions. In such instances, the evidence integration narrative should be clear and transparent in articulating the rationale for the final decision(s).[52]

NASEM (2011) went on to criticize the 2010 Draft Assessment for the lack of a clearly articulated framework for establishing causation on the "basis of the weight and strength of the evidence."

EPA reports that it implemented NASEM's recommendations by evaluating studies related to each endpoint using "a common evidence integration framework for determinations of causality" with rationales described in the integrated summaries of evidence (Appendix D of the 2022 Draft Assessment). Indeed, EPA has developed a framework for weighing evidence, informed by Bradford Hill postulates (as recommended by NASEM 2011) as presented in the IRIS Handbook and the 2022 Draft Assessment. However, as applied, the integration process requires substantial

[51] Cancer Guidelines §1.3.3 (2005), 1-11.
[52] Cancer Guidelines at 11-26.

scientific judgment, and the 2022 Draft Assessment does not clearly describe the way in which evidence was synthesized and integrated to reach its determinations of causality.

The opaque and inconsistent process of evidence integration in the 2022 Draft Assessment is exemplified in EPA's treatment of the evidence for nasopharyngeal cancers (NPCs) relative to lymphohematopoietic malignancies. In both cases, EPA concluded that the "**evidence demonstrates**" that formaldehyde inhalation causes NPCs and myeloid leukemia, "given appropriate exposure circumstances."[53] However, the body of evidence for these two cancers are quite different and based on EPA's own criteria, should not have the same hazard determination.

For a classification of "Evidence demonstrates," the IRIS Handbook requires "a strong evidence base demonstrating that [chemical] exposure causes [health effect] in humans."[54] This conclusion is reached if there is "***robust*** human evidence supporting an effect" or if there is moderate human evidence couple with robust animal evidence and strong mechanistic evidence that the findings in animals are relevant to humans. It also states, "Most notably, an MOA interpreted with reasonable certainty would rule out alternative explanations."[55]

In the case of NPCs, nasal tumors occur in animals and there are plausible MOAs that have supporting evidence (primarily, cytotoxicity and regenerative proliferation) to support the epidemiological findings. In contrast, myeloid leukemia has no positive animal evidence nor biologically plausible MOA.

EPA purported that its causal conclusion regarding LHMs was "based on multiple epidemiologic studies that found associations with different exposure metrics, and which were **supported by mechanistic studies in exposed humans that provided biological support for genotoxic and immunologic changes in peripheral blood cells**" (emphasis added).[56] As discussed above, the human evidence is neither consistent nor strong, there are no lymphohematopoietic cancers observed in animals, and perhaps most importantly, there is no biologically plausible MOA.

In fact, EPA states early in the 2022 Draft Assessment: "Generally, evidence supporting the development of LHP cancers after formaldehyde inhalation has not been observed in experimental animals (i.e., rodents), including a well-conducted, chronic cancer bioassay in two species, a similar lack of increased leukemias in a second rat bioassay, and multiple mechanistic evaluations of relevant biological changes, including genotoxicity (i.e., inadequate evidence). The exact mechanism(s) leading to cancer formation outside of the respiratory tract are unknown."[57]

As discussed in these comments, EPA relies heavily on just a few flawed studies (Zhang et al. 2009, 2010; Lan et al. 2015) which "reported effects on myeloid progenitor cells cultured from peripheral blood of exposed workers compared to cells cultured from controls without

[53] 2022 Draft Assessment at 1-338, 1-542.
[54] IRIS Handbook at 11-22.
[55] IRIS Handbook at 11-22.
[56] 2022 Draft Assessment (Appendix) at D-30.
[57] 2022 Draft Assessment at lv.

occupational formaldehyde exposure."[58] These studies have since been refuted in the literature (Mundt et al., 2017).

2.0 The 2022 Draft Formaldehyde IRIS Assessment does not adhere to the 2020 Draft IRIS Handbook.

> "The [IRIS] handbook should clearly define the roles of mechanistic data and other supporting data in evidence integration and throughout the entire IRIS assessment development process."
>
> – NASEM 2022

2.1 The 2022 Draft Assessment does not follow guidance in the IRIS Handbook.

The 2022 Draft Assessment makes no specific reference to the IRIS Handbook with the exception of a single footnote.[59] However, some of the general processes mirror, at least in the part, the IRIS Handbook. In other parts, it deviates from the IRIS Handbook more substantively.

There are several places in the 2022 Draft Assessment with language and tables that are borrowed from the IRIS Handbook, but, in some cases, subtle changes were made that, while easily missed, are not unsubstantial.

For example, "Table III. Information most relevant to describing primary considerations informing causality during evidence syntheses,"[60] which reflects EPA's methodology for evidence synthesis, is taken largely from the IRIS Handbook.[61] Almost the entire table was copied into the 2022 Draft Assessment verbatim, with the exception of the IRIS Handbook's row for "study confidence" (presumably because the 2022 Draft Assessment describes this elsewhere). Critically, however, there several omissions regarding guidance on applying the Bradford Hill postulates, as follows:

In the IRIS handbook row for consistency, the following statement appears: "It may be helpful to **consider the potential for publication bias** and to provide context to interpretations of consistency."[62] This sentence – and this sentence alone – is omitted from this row in the 2022 Draft Assessment. There is no reason why this sentence would need to be removed, and, in fact, it is an important consideration given that publication bias is highly prevalent in the environmental health literature.

In the strength section of the same table, the IRIS Handbook states, "**Note that a synthesis includes consideration of null (or negative) as well as positive results.**"[63] There is no such statement regarding "null" findings in the corresponding table in formaldehyde. Again, it is

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[58] 2022 Draft Assessment at 1-520.
[59] 2022 Draft Assessment at xxi.
[60] 2022 Draft Assessment at xxxv.
[61] IRIS Handbook at 9-3-9-5.
[62] IRIS Handbook at 9-3.
[63] IRIS Handbook at 9-4. (emphasis added).

unclear why the 2022 Draft Assessment authors would remove this statement, as a comprehensive and balanced evidence synthesis should consider the entire body of the evidence, including both positive and negative studies, in determining the likelihood for a causal effect.

Finally, in the row discussing coherence, the IRIS Handbook states: "If an expected coherence between findings is not observed, **possible explanations should be explored including the biology of the effects** as well as the sensitivity and specificity of the measures used."[64] This is not present in the corresponding 2022 Draft Assessment table. Again, with formaldehyde, understanding the biology of effects is key to interpreting the science.

2.2 The 2022 Draft Assessment does not consider IRIS Handbook recommendations regarding MOA.

While the IRIS Handbook does not explicitly require organization around MOA hypotheses, it does state that "hypothesized MOAs that lack scientific consensus" are an example of science issues that should be included in problem formulation.[65] Later in the IRIS Handbook, EPA states: "It is important to review and assess the likely impact of potentially controversial mechanistic issues (e.g., evidence a chemical is mutagenic, the human relevance of alpha2-globulin) on assessment conclusions **early in the process**" (emphasis added).[66]

Given that EPA acknowledges in the 2022 Draft Assessment that there are no known MOAs for formaldehyde and lymphohematopoietic malignancies, EPA should have deprioritized these malignancies for assessment.

EPA's treatment of mechanistic data continues to be problematic. As EPA notes on page xxxviii, "the lack of mechanistic data explaining an association did not discount results from human or animal health effect studies." While very strong, consistent and positive evidence in animals and humans, indicative of an effect, is often sufficient to make some conclusions on the likelihood of human health risk, in most cases, there is some inconsistency both within and across the animal and human streams of literature, which makes mechanistic information exceedingly important. EPA should give more weight to mechanistic information, particularly when it exists and does not support a human-relevant mechanism. The Agency for Toxic Substances and Disease Registry (ATSDR) echoed this concern in their interagency review comments.[67]

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[64] IRIS Handbook at 9-4. (emphasis added)
[65] IRIS Handbook at 2-5.
[66] IRIS Handbook at 10-2.
[67] Agency for Toxic Substances and Disease Registry (ATSDR), Comments on the Interagency Science Consultation Draft IRIS Assessment of Formaldehyde–Inhalation dated December 2021 (Jan. 5, 2022) available at https://ordspub.epa.gov/ords/eims/eimscomm.getfile?p_download_id=544465 [hereinafter ATSDR 2022]

3.0 The 2022 Draft Assessment conclusions are speculative and lack scientific confidence because EPA applied a flawed and subjective study evaluation method, especially in the analysis and interpretation of the epidemiology data.

As described above, the NASEM (2011) Committee stated that the methods for critically evaluating individual studies in the 2010 Draft Assessment were unclear. In the NASEM 2011 and NASEM 2014 reviews, the respective Committees recommended developing tools to assess risk of bias and other issues related to study quality. NASEM stated:

> EPA will need to develop a clear set of criteria for judging the relative merits of individual mechanistic, animal, and epidemiologic studies for estimating human dose-response relationships.
>
> – NASEM 2014

While EPA has made progress in this area, the study evaluations presented in the 2022 Draft Assessment need improvement and reflect two distinct but related issues: 1) several important deficiencies remain in the evaluation framework provided in the IRIS Handbook and 2) the 2022 Draft Assessment fails to follow the IRIS Handbook.

With respect to first point, the IRIS Handbook is still a draft, and it is unclear if the public comments and NASEM peer review critiques have been incorporated into EPA's current systematic review approach for IRIS. While the NASEM committee praised sections of the IRIS Handbook, they also remained critical – particularly with regard to the study evaluation framework. The Committee noted that while EPA had addressed many of the NASEM (2011) critiques, some aspects of the process of study evaluation remained unclear and potentially problematic, including how the study evaluation confidence ratings would be used by EPA in making hazard determinations. The Committee stated:

> The handbook augments study evaluation to consider, in both human and animal studies, the additional quality assessment items of sensitivity and reporting quality. The inclusion of these additional quality assessment items was anticipated in NASEM (2014) and has precedent in animal toxicological studies (Hooijmans et al., 2018; NTP 2019[68]). However, **the distinctions among the concepts of risk of bias, reporting quality, and sensitivity are not always clearly delineated in the handbook**, and some considerations have clear overlap with more established concepts in systematic review. **This mixing of concepts is prone to inhibit transparency and reproducibility in documenting how each concept is incorporated into domain judgments and study confidence ratings**. Operationally, these concepts are sometimes considered collectively when evaluating domains, complicating an ultimate evaluation where elements of one concept can be incorporated into a judgment in multiple domains and be simultaneously cited as their

[68] NTP (National Toxicology Program). 2019. Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. March 4, 2019. Research Triangle Park, NC Office of Health Assessment and Translation (OHAT), Division of the National Toxicology Program, National Institute of Environmental Health Sciences.

> own evaluation concerns. As such, it is difficult to see exactly how the procedure in the handbook would avoid "double counting" a single issue in multiple domains…" (emphasis added).[69]

Indeed, the NASEM (2022) concern is borne out in the 2022 Draft Assessment; EPA's analysis and interpretation of epidemiology data in the 2022 Draft Assessment is flawed. Not only does the study evaluation framework deviate from that required in the IRIS Handbook, but also EPA does not clearly communicate the results of its study evaluation. EPA also fails to consistently apply its own IRIS rating system for the robustness of exposure categorization, fails to thoroughly consider exposure latency, implements a highly subjective methodology for evaluating study reporting, biases, and sensitivity, and selectively interprets studies according to particular exposure metrics. All of these oversights lead to a lack of confidence in EPA's conclusions. Specific issues are described in detail below.

3.1 The study evaluation framework in the 2022 Draft Assessment deviates from the IRIS Handbook.

The general description provided in the 2022 Draft Assessment is as follows:

> Study methods were evaluated to assign a level of confidence in the results of the study with respect to the hazard question under consideration. The study confidence levels were *high*, *medium*, and *low* confidence, and *not informative*, and are presented as italicized text in the body of the assessment. These evaluations were performed on a health outcome-specific basis, rather than a study-specific basis; thus, a single study was sometimes evaluated multiple times for different endpoints, sometimes involving slightly different considerations.[70]

First, the actual process of arriving at these confidence conclusions are not well described, particularly for epidemiological studies. In the description of evaluation of individual observational studies, Appendix A states that "[c]onfidence classifications were developed for each study by integrating the judgements for each category of bias and sensitivity: population selection, information bias, confounding, analysis, and other (sensitivity)."[71]

For each of these categories of evaluation, only a short description of the considerations is provided. For example, in the "other category", the formaldehyde draft states only that "[o]ther considerations not otherwise evaluated [included]: Sensitivity of study (exposure levels, exposure contrast, duration of follow-up, sensitivity of outcome ascertainment)." [72]

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[69] National Academies of Sciences, Engineering, and Medicine. 2022. A Review of U.S. EPA's ORD Staff Handbook for Developing IRIS Assessments: 2020 Version. Washington, DC: The National Academies Press. https://doi.org/10.17226/26289 at 55 [hereinafter NASEM 2022]. (emphasis added).
[70] 2022 Draft Assessment at xxvi.
[71] 2022 Draft Assessment (Appendix) at A-232.
[72] 2022 Draft Assessment (Appendix) at A-233.

The graphical output of the study evaluation process for epidemiological studies appears as follows:

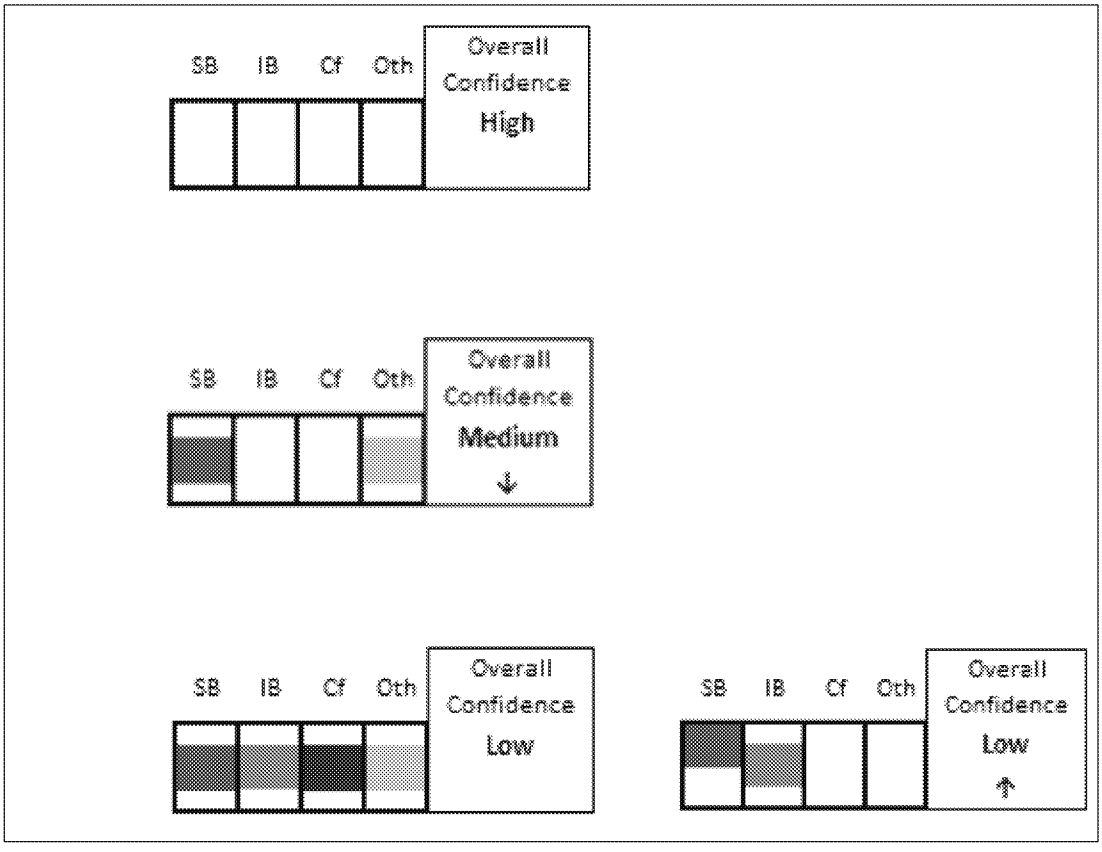

Figure II. Summary depictions of evaluation of epidemiology studies.

The extent of column shading reflects the degree of limitation. Different colors are intended to visually distinguish the columns and have no other meaning. The direction of anticipated bias is indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate). Panel A: *High* confidence study; Panel B: *Medium* confidence study with likely attenuated effect estimate; Panel C: Two possible examples for a *low* confidence study. Color blocks that straddle the midline indicate that the direction of bias is unknown or not predictable. The depiction on the right indicates that selection bias (SB) likely resulted in an overestimate of the effect estimate, indicated by the colored block above the midline. Abbreviations: SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis.

This depiction of EPA's evaluation of study bias and quality, used in the Appendix tables that describe the individual study evaluations, is difficult to read and interpret. In contrast, the IRIS Handbook process for study evaluation (and its graphical representation) is different.

The IRIS Handbook describes the epidemiology evaluation framework as follows (and as pictured in the example figure for evaluating studies reproduced below):

> The principles and framework used for the evaluation of epidemiology studies examining chemical exposures are adapted from the principles in the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I), modified for use with the types of studies more typically encountered in environmental and occupational epidemiology rather than clinical interventions (Sterne et al., 2016). The evaluation domains for IRIS's adapted approach are exposure measurement, outcome ascertainment, participant selection, confounding, analysis, study sensitivity, and selective reporting. For each domain, "core," "prompting," and follow-up questions are provided below, and are used to guide the development of assessment specific considerations. Reporting quality and risk of bias are considered during the evaluation of each domain, and the rating may be lowered when information needed to evaluate a domain is not available."[73]

The IRIS Handbook framework describes eight separate domains relative to the four domains assessed in the 2022 Draft Assessment. While the 2022 Draft Assessment appears to incorporate many of the same general study characteristics, because these characteristics are collapsed into fewer categories, it is difficult to determine why a particular rating was assigned to that category.

[73] IRIS Handbook at 6-10.

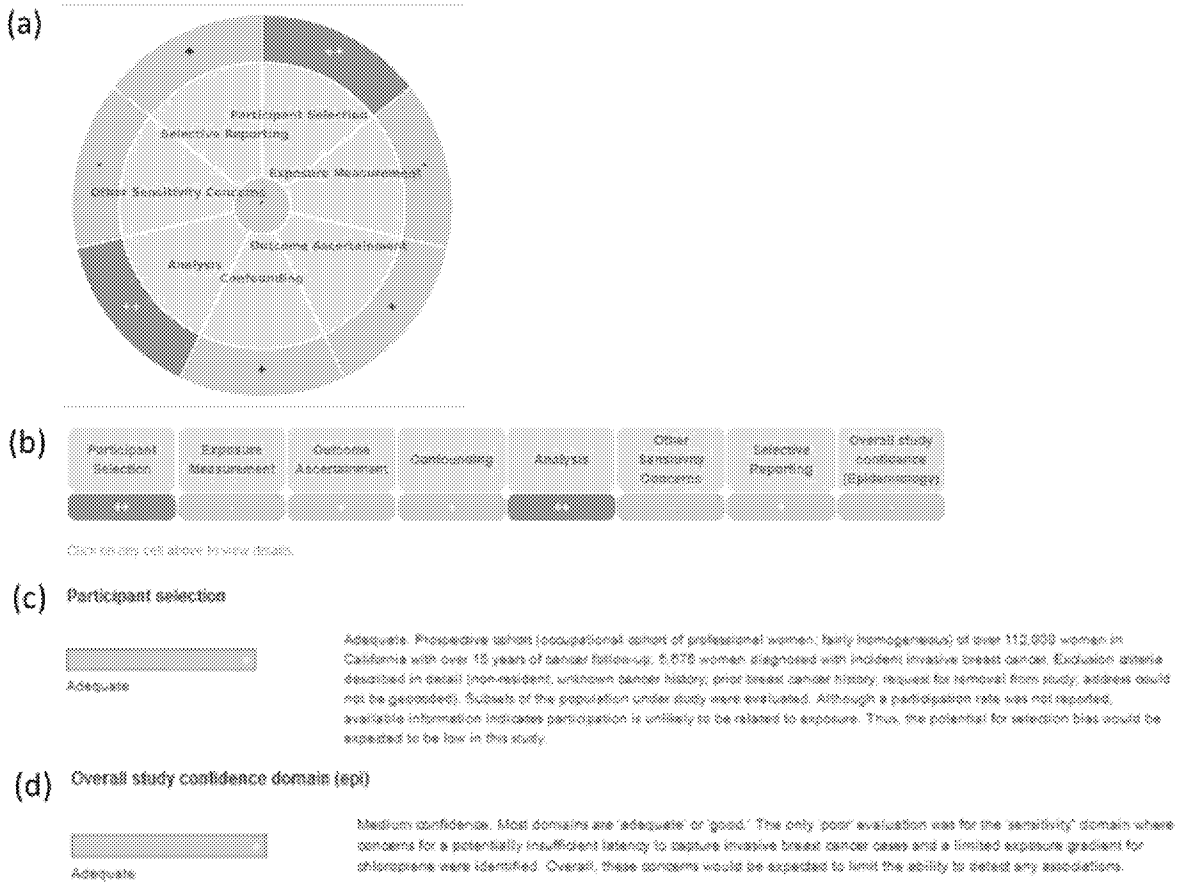

Figure 6-2. Examples of study evaluation displays at the individual level. (a) A

3.2 The study evaluation findings are not clearly communicated.

The results of the individual study evaluations are provided in Appendix A of the 2022 Draft Assessment. The supplemental tables providing the study evaluation results are disorganized and difficult to follow, with primary analyses and follow-up studies presented in the same long, sprawling cells. It is thus difficult to parse out why each study received ratings for each of the categories and/or why it was assigned a particular confidence score. This issue is most noticeable in instances of epidemiological cohorts with multiple "related" studies including follow-up studies and re-analyses.

For example, on page A-697, the Coggon et al. (2014) study is presented at the top of the cell while the multiple follow up studies are listed below, but only a single study confidence score is given. Is this meant to imply these studies were identical in conduct and reporting? As an example of the reverse situation, on page A-691, Beane Freeman et al. (2009) and (2013) are presented alongside numerous related studies, including a reanalysis by Checkoway et al. (2015). Beane Freeman et al. (Both studies? One or the other? One cannot tell) received a high

confidence rating for most endpoints and a medium confidence for sinonasal cancer. Checkoway et al. (2015), which is based on the same data, received a low confidence rating.

As another example of poor depiction of EPA's decision-making (and the results of its evaluation), is the depiction of potential confounders in the tables of human studies of cancer. Regarding the analysis of confounding due to co-exposures, EPA states that "specific chemical and occupational exposures … which were reported to be associated with [lymphohematopoietic] … cancers are **bolded.**"[74] Examples of potential co-exposures included in the evaluation of studies include pharmaceuticals (chemotherapeutic drugs), biological agents, radiation, and chemical exposures (i.e., benzene, 1,3-butadiene, 2,3,7,8-tetrachlorodibenzo-para-dixoin, etc.). However, these risk factors are not consistently bolded and identified as confounders across the individual studies, despite noting possible confounding due to co-exposures (see Blair et al. 2001 – Table A-106). Given the abbreviated nature of the text in these tables, EPA's assessment of whether a study adjusted for potential confounders is not always clear. Due to these inconsistencies in the descriptions, evaluating potential confounding across studies is confusing. Thus, EPA's results are difficult to replicate.

3.3 EPA does not consistently apply its own IRIS rating system for the robustness of exposure categorization in epidemiological studies.

As part of its study evaluation process, the EPA developed a seemingly *de novo* framework for categorizing exposure assessment methods of the identified studies into four groups (A through D), intending to indicate greater or lesser reliability and sensitivity of the exposure surrogates. This specific framework (i.e., A through D ratings) is not provided in the IRIS Handbook, which provides relatively vague guidance for evaluating and classifying the quality of study exposure surrogates.[75]

The framework in the 2022 Draft Assessment allows a high level of reviewer subjectivity during the evaluation. For example, the main study design features for Group A cohort and case controls studies are: "Industrial settings with extensive industrial hygiene data used to determine levels of exposure (and variability within a worksite); job exposure matrix takes into account variability by time and job/task" and "Highly exposed professions (embalmers) with comparison to general population, or with measures capturing variability within the cohort."[76] However, distinguishing variability in exposure levels within a study population remains poorly defined and the lack of a rigorous definition lends to inconsistent classifications. Several methodological limitations or interpretational inconsistences were noted for studies evaluating myeloid leukemia, including but not limited to the following:

- Beane Freeman et al. (2009) relied on individual-level exposure estimates based on job titles and tasks from 2,000 air samples measurements collected from 1960 to

[74] 2022 Draft Assessment (Appendix) at A-684.
[75] IRIS Handbook at 6-14.
[76] 2022 Draft Assessment (Appendix) at A-679-680

1980. Various time-dependent exposure metrics were estimated from the relatively robust industrial hygiene data including "peak" exposure, time-weighted average exposure intensity, cumulative exposure, and average intensity. Though their surrogate for "peak" exposure was novel, EPA appropriately classified this study as Group A.

- Also included in Group A, however, was Hauptmann et al. (2009), a nested case control analysis of death certificate information (i.e., an alternative statistical analysis and interview data from next of kin and coworkers for assigning exposure categories. Interview questions included an estimate of frequency of embalmings that might have been performed by the decedent by decade for each job held at least five years. Additional information on ventilation factors and workplaces practices was considered. The questionnaire responses were linked to measurement data from an exposure-assessment experiment and a predictive model was developed. However, the comparability between historical exposure scenarios involving embalmers and formaldehyde application and the scenarios conducted in the exposure experiment were not reported. Ultimately, the actual exposure to formaldehyde of any funeral director or embalmer was not known and surrogates based on number of embalming could not be verified. Nevertheless, EPA apparently attempted to generate a definition of exposure that specifically allowed the classification of Hauptmann et al. (2009) as Group A, i.e., and as noted above, "[h]ighly exposed professions (embalmers) with comparison to general population, or with measures capturing variability within the cohort."[77] Hauptman et al. (2009) satisfies neither.

- Inexplicably, and in contrast to Hauptmann et al. (2009), EPA classified the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study (Saberi Hosnijeh et al. 2013) as Exposure Group C ("Industrial settings that are only able to use duration as a way to distinguish variability in exposure")[78] even though the paper is clear that a job-exposure matrix (JEM) was used ("Occupational exposures were estimated by linking the reported occupations to a general population job exposure matrix (ALOHA-JEM)," Saberi Hosnijeh et al. 2013). Why the methodology as described by the study investigators was discounted by EPA is not explained, and again illustrates how the review methodology allows for potentially subjective assessment leading to selective inclusion and de-selection of studies.

- The subjective nature of the study confidence assessment framework was particularly apparent regarding the exposure assessment categorization of Checkoway et al. (2015) into Group D. Epidemiological studies were classified as Group D due to their lack of exposure data to distinguish variability in exposure or due to few exposed cases. In contrast, Checkoway et al. (2015) was classified in Group D due to "methods of exposure assessment rated as higher quality but downgraded due to

[77] 2022 Draft Assessment (Appendix) at A-680.
[78] 2022 Draft Assessment (Appendix) at A-680.

methods used by study authors which were likely to introduce bias." Ironically, Checkoway et al. (2015) reanalyzed the same cohort data from Beane Freeman et al. 2009, and provided additional analyses not reported by the original investigators. This included an additional exposure metric for "peak" exposure that was more in line with industrial hygiene definitions for "peak" (likely excursions above an arbitrary or typical level versus relative excursions from any baseline). The results based on the more conventional "peak" exposure metric aligned with those derived by Beane Freeman et al. (2009) except for their novel approach to "peak" exposure (NB: "peak" appears in quotes because no peak exposure data were available and therefore it is unknown which cohort members – including those subsequently developing and dying of acute myeloid leukemia – ever had sustained any true peak exposure to formaldehyde). Ironically, the more thorough analysis of the same data was "downgraded" due to one relatively minor (but highly enlightening) "sensitivity test" of the novel "peak" definition in Beane Freeman et al. (2009).

3.4 EPA does not thoroughly consider exposure latency.

Latency is emphasized as an important consideration when evaluating potential epidemiologic associations between formaldehyde exposure and LHMs. However, the rationale for prioritizing this consideration is unclear as latency estimates vary widely for different LHMs. The absence of an MOA introduces further difficulty when estimating potentially relevant occupational exposures and, therefore, latency. Finally, latency adjustments in many cohorts and nested case-control studies were relatively crude (i.e., incorporating lag period of 2 years).

3.5 EPA's subjective methodology for evaluating study reporting, biases and sensitivity extends to the overall confidence ratings.

Checkoway et al. (2015) and Beane Freeman (2009) are rated differently, despite using the same data. Checkoway was downgraded for "low sensitivity" based on possible "bias away from the null," yet Checkoway et al. (2015) is arguably a stronger study considering its treatment of quality domains of higher importance.

3.6 EPA selectively interprets studies according to particular exposure metrics (i.e., peak exposure).

In some instances, the high confidence ratings in the epidemiological studies are warranted based on the overall study evaluation framework described; however, the interpretation of the relevant risk estimates for LHMs were flawed (i.e., the application of the study evaluation was not problematic, but the interpretation of the findings was). For example, Beane Freeman et al. (2009) found inconsistent associations between various exposure metrics and LHMs. Specifically, whereas peak exposure was associated with a statistically significant increased risk of all LHMs and Hodgkin lymphoma, cumulative exposure and average intensity of formaldehyde exposure demonstrated no associations. EPA appears to have interpreted this study as evidence of an effect, and the effect estimates were classified as *high confidence*. The use of peak exposure as the primary exposure metric of interest is subject to many limitations (e.g., see Checkoway et al., 2019). Peak exposure, relative to cumulative exposure, is a crude surrogate for a worker's time-dependent exposure history. Given the discrepancies regarding

associations between peak exposure and cumulative exposure and LHM risk, the overall evidence for a causal association is weakened.

B. ENDOGENOUS PRODUCTION OF FORMALDEHYDE

EPA does not fully incorporate the role of endogenous production of formaldehyde in drawing conclusions regarding the potential for health effects from exogenous inhalation exposure.

Unlike other authoritative bodies, EPA continues to claim that formaldehyde's effects are not limited to the site of contact, while offering no evidence to support an MOA to explain these distal effects. Due to its chemical reactivity, formaldehyde does not penetrate deep within the tissue upon contact and does not reach the systemic blood circulation. Therefore, EPA and other regulatory and authoritative agencies conclude that there is a lack of penetration of formaldehyde beyond site of contact. However, EPA does not consider this fully when concluding that there are effects at distal sites.

In the review of the 2010 Draft Assessment, NASEM (2011) identified several issues related to the toxicokinetics and mode of action for formaldehyde that needed to be addressed in the revision of the draft of assessment. While the previous assessment and the current assessment provide a discussion of formaldehyde toxicokinetics, the 2022 Draft Assessment does not provide a discussion or consideration of when exogenous formaldehyde exposure appreciably alters normal endogenous formaldehyde concentrations, as recommended by NASEM.[79] This evaluation is critical in drawing conclusions regarding the potential for health effects following inhalation exposure of formaldehyde. In its 2011 report NASEM noted that "The endogenous production of formaldehyde complicates the assessment of the risk associated with formaldehyde inhalation and remains an important uncertainty in assessing additional dose received by inhalation, particularly at sites beyond the respiratory tract."[80]

NASEM recommended that EPA complete an analysis of variability and uncertainty in measuring and predicting target-tissue formaldehyde concentrations among species. As recommended by NASEM (2011), only with such an analysis can one begin to identify and address openly and transparently the question of how much added risk for an endogenous compound is acceptable.[81] However, EPA did not conduct this evaluation in the 2022 Draft Assessment.

Formaldehyde is a classic example of a chemical for which the beneficial and adverse effects can only be considered in the context of dose-dependent transitions. Endogenous formaldehyde is essential to life while high exogenous concentrations result in adverse effects. There are numerous studies that provide evidence that exogenous formaldehyde does not move past the portal of entry in multiple species (i.e., rats and non-human primates) following both acute and

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[79] NRC (National Research Council). 2011. Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde. Washington, DC: The National Academies Press. https://doi.org/10.17226/13142.

[80] NASEM 2011 at 4.

[81] NASEM 2011.

subchronic inhalation exposure across a range of air concentrations (0.001 ppm to 15 ppm) Kleinnijenhuis et al. 2013[82]; Lu et al. 2010[83], Lu et al. 2011[84]; Edrissi et al. 2013[85]; Moeller et al. 2011[86]; Lai et al. 2016[87]; Yu et al. 2015[88]; Leng et al. 2019[89]).

These studies have been conducted in response to NASEM's questions around the toxicokinetics of formaldehyde, as well as the impact of exogenous exposure on endogenous levels of formaldehyde, both of which are critical in conducting a risk assessment. Despite decades of research using highly sensitive methods, EPA continues to derive a risk for myeloid leukemia in the absence of even a hypothesized MOA and with clear toxicokinetic evidence that formaldehyde does not move beyond the portal of entry.

In addition to the investigation of the distribution of formaldehyde following inhalation exposure, the studies noted above (Lu et al. 2010, 2011; Lai et al. 2016) involve the application of methods that have been developed that allow for a definitive differentiation of exogenous- and endogenous-specific DNA monoadducts, DNA-DNA adducts, and protein using methods of 13CD2-isotope labeling of hydroxymethyl-dG (HmdG) or hydroxymethyl-dA (HmdA) (in vitro derivative of reversible hydroxy methyl reaction products formed in vivo). Using these sensitive methods, Lu et al. 2010, Lu et al. 2011 and Lai et al. 2016 provide quantitative data on the endogenous and exogenous concentrations of formaldehyde at the portal of entry following inhalation exposure and provide evidence regarding when exposures to exogenous formaldehyde are sufficient to disrupt formaldehyde homeostasis at the portal of entry. This understanding has not been incorporated into the qualitative or quantitative evaluations conducted in the 2022 Draft

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[82] Kleinnijenhuis AJ, Staal YC, Duistermaat E, Engel R, Woutersen R. 2013. The determination of exogenous formaldehyde in blood of rats during and after inhalation exposure. Food Chem Toxicol. 52:105–112.

[83] Lu K, L. Collins, R. Hongyu, E. Bermudez, J Swenberg. 2010. Distribution of DNA adducts caused by inhaled formaldehyde is consistent with induction of nasal carcinoma but not leukemia, Toxicol. Sci., 116, 441-451.

[84] Lu K, B. Moeller, M. Doyle-Eisele, J. McDonald, and J. Swenberg. 2011. Molecular dosimetry of N2-hydroxymethyl-dG DNA adducts in rats exposed to formaldehyde. Chem. Res. Toxicol., 24, 159-161.

[85] Edrissi B, K. Taghizadeh, B. Moeller, D. Kracko, M. Doyle-Eisele, J. Swenberg, and P. Dedon, 2013. Dosimetry of N6-formyllysine adducts following [13C2H2]-formaldehyde exposures in rats, Chem. Res. Toxicol., 2013, 26, 1421-1423.

[86] Moeller B.C., K. Lu, M. Doyle-Eisele, J. McDonald, A. Gigliotti, and J. Swenberg. 2011. Determination of N2-hydroxymethyl-dG adducts in the nasal epithelium and bone marrow of nonhuman primates following 13CD2-formaldehyde inhalation exposure, Chem. Res. Toxicol., 2011, 24, 162-164.

[87] Lai Y, R. Yu, H. Hartwell, B. Moeller, W. Bodnar, and J. Swenberg. 2016. Measurement of endogenous versus exogenous formaldehyde-induced DNA-protein crosslinks in animal tissues by stable isotope labeling and ultrasensitive mass spectrometry, Cancer Res., 2016, 76, 2652-2561.

[88] Yu R, Lai Y, Hartwell HJ, Moeller BC, Doyle-Eisele M, Kracko D, Bodnar WM, Starr TB, Swenberg JA. 2015. Formation, Accumulation, and Hydrolysis of Endogenous and Exogenous Formaldehyde-Induced DNA Damage. Toxicological Sciences, 146(1): 170-182.

[89] Leng J, Liu C, Hartwell HJ, Yu R, Lai Y, Lu K, Leibold E, Swenberg JA. 2019. Evaluation of inhaled low-dose formaldehyde-induced DNA adducts and DNA-protein cross-links by liquid chromatography-tandem mass spectrometry. Arch Toxicol 93(3):763-773.

Assessment yet are critical to understanding the potential for health effects following exogenous exposure, as noted by NASEM (2011).

The 2022 Draft Assessment includes numerous citations to Dr. Kun Lu's work, which as noted above, involved the use of a unique, sensitive, and robust stable isotope labeling and mass spectrometry (SILMS) methods and formaldehyde-specific biomarker data to distinguish between N2-hm-dG adducts from exogenous (inhaled) formaldehyde and N2-hm-dG adducts from endogenous formaldehyde (2022 Draft Assessment, 1-9). Dr. Lu's work provides a method to unambiguously evaluate the risk of inhaled formaldehyde when substantial endogenous formaldehyde is always present – a method for which EPA failed to account in the 2022 Draft Assessment.

In developing these analytical methods, Dr. Lu and his lab generated rich datasets over the span of a decade. EPA's failure to integrate these datasets into the 2022 Draft Assessment was a serious oversight, ignores what is clearly the best available science, and represents a missed opportunity to use Dr. Lu and his colleagues' rigorous results to improve evidence-based assessment of inhaled formaldehyde under the substantial background of endogenous formaldehyde (EPA-HQ-ORD-2010-0396).

As described more fully in his comments (EPA-HQ-ORD-2010-0396), Dr. Lu underscores numerous, major issues with the 2022 Draft Assessment's treatment of his work. He also makes several recommendations to EPA to correct each oversight that are needed to improve the evidence-based risk assessment of inhaled formaldehyde given the substantial background of endogenous production.

III. MYELOID LEUKEMIA

A. The scientific evidence does not support EPA's conclusion that "evidence demonstrates" formaldehyde causes myeloid leukemia

In the 2022 Draft assessment, EPA concluded that "the **evidence demonstrates** that formaldehyde inhalation causes myeloid leukemia in humans given appropriate exposure circumstances."[90] This conclusion mirrors the conclusion in the 2010 Draft Assessment. In its revised assessment of lymphohematopoietic (LHP) malignancies, EPA no longer categorizes LHPs as one large group, as recommended by NASEM (2011). EPA, however, continues to lump two distinct cancers -- acute myeloid leukemia (AML) and chronic myeloid leukemia (CML), into myeloid leukemia.

NASEM's recommendations pertaining to clear evidence evaluation approaches and standardized, well-described evaluations of the weight-of-the-evidence conclusions have only been partially addressed. While EPA has made some strides in its methodology, EPA's overall hazard assessment conclusions are not supported by the available epidemiological, animal or MOA literature.

Briefly, in assessing LHPs EPA purported that the set of high confidence epidemiological studies are consistent and demonstrate strong magnitudes of effect and dose-response gradients. EPA

[90] 2022 Draft Assessment at 1-542.

also noted that there was "reasonable confidence that alternative explanations are ruled out, including chance, bias, and confounding within individual studies or across studies." However, as discussed below, the epidemiological evidence does not in fact demonstrate a clear or convincing relationship between formaldehyde and any LHP malignancy. The EPA described the animal evidence as indeterminate when high quality animal studies do not support that formaldehyde causes LHP cancers. Finally, the EPA described the evidence on the mode of action as indeterminate when high quality data exist that refuted the hypothesis that formaldehyde interacts with tissue distant from the portal of entry. Specific comments regarding the epidemiological literature are provided below, followed by a discussion of MOA and animal evidence.

1. The EPA's conclusion that the epidemiological evidence is "robust" for formaldehyde exposure and myeloid leukemia is not scientifically supported.

In brief, EPA relied on a set of purportedly high confidence studies that included the NCI formaldehyde manufacturers and users cohort (Beane Freeman et al. 2009), the NCI nested case-control study of deceased embalmers (Hauptmann et al. 2009) and the NIOSH garment workers cohort (Meyers et al. 2013). These studies together formed the basis of its conclusion that the epidemiological data was robust; specifically:

> Human studies provided robust evidence for myeloid leukemia [...] based on epidemiology studies of occupational formaldehyde levels either in specific work settings (e.g., cohort studies) or in case-control studies. Taken together, based on the robust human evidence for these cancers from studies that reported increased risk in groups exposed to occupational formaldehyde levels, the evidence demonstrates that formaldehyde inhalation causes myeloid leukemia in humans, given appropriate exposure circumstances.[91]

> The causal evaluation for formaldehyde exposure and the risk of developing or dying from myeloid leukemia placed the greatest weight on five particular considerations: (1) the generally consistent increases in risk observed across a set of high and medium confidence independent results from epidemiology studies of occupational formaldehyde levels using varied study designs and populations; (2) the strength of the association showing a 1.5- to 3-fold increase in risk in studies with higher quality exposure assessment; (3) the reported exposure-response relationships showing that increased exposure to formaldehyde were associated with increased risk of dying from myeloid leukemia; (4) a biologically coherent temporal relationship consistent with a pattern of exposure to formaldehyde and subsequent death from myeloid leukemia allowing time for cancer induction, latency, and mortality; and (5) reasonable confidence that alternative explanations are ruled out, including chance, bias, and confounding within individual studies or across studies.[92]

[91] 2022 Draft Assessment at 1-435-1-436.
[92] 2022 Draft Assessment at 1-452.

Contrary to EPA's assertions, epidemiological studies of occupational groups historically highly exposed to formaldehyde generally do not demonstrate statistically significantly increased rates of myeloid leukemia or more specifically AML and CML.

- No statistically significant excess risk above background rates of myeloid leukemia are reported in the three cohort studies (Beane Freeman et al. 2009; Meyers et al. 2013 Coggon et al. 2014), including two which were rated as having "effect estimates classified with high confidence" (Beane Freeman et al., 2009; Meyers et al. 2013) and one which was rated as having moderate confidence (Coggon et al. 2014)
- Results from studies with arguably just as high or higher quality observed no significant increases in AML, CML, or myeloid leukemia (Saberi Hosnijeh et al. 2013, Talibov et al. 2014, Checkoway et al. 2015)
- Results do not indicate consistent increases in risk across exposure measures in the studies rated "high confidence" (Hauptmann et al., 2009; Beane Freeman et al., 2009; Meyers et al. 2013)

Thus, there is no "reasonable confidence that alternative explanations" (i.e., chance and bias) can be ruled out. In fact, EPA's "five particular considerations" 1, 2 and 5 quoted above do not support causality.

In synthesizing the results of the epidemiology studies, EPA emphasized consistency, magnitude of effects, and dose-response gradients. For example, the EPA reported "consistent increases in risk across a set of high and medium confidence, independent studies with varied study designs and populations."[93] The estimates of relative risk of myeloid leukemia, however, were not consistent within or between studies in relation to various formaldehyde exposure metrics. In the 2022 Draft Assessment, EPA stated:

> While it is not known which of these exposure metrics is of greatest biological relevance for myeloid leukemia, all of the exposure metrics reflect different aspects of increased exposure to formaldehyde and associations with increased risks of myeloid leukemia. As the different measures of exposure are all likely to be correlated with each other, it may not be possible at this time to single out one exposure metric as more biologically meaningful than another. It appears that these various trend results reflect some true underlying exposure-response relationship.[94]

This excerpt points to a fundamental issue regarding consistency of evidence using different measures of exposure. As a general statement, it is true that different measures of exposure ***within*** a study may be correlated with each other; therefore, when a disease outcome is analyzed, associations are seen between the different exposure measures and the disease. This pattern is not seen, however, in studies of formaldehyde exposure and myeloid leukemia. Most of the studies report associations with one exposure metric but not other (sometimes very similar) exposure metrics.

[93] 2022 Draft Assessment at 1-542.
[94] 2022 Draft Assessment at 1-449.

A conclusion of consistent associations between formaldehyde exposure and myeloid leukemia is not scientifically justifiable when the observed associations between formaldehyde measures and myeloid leukemia differ according to exposure metrics ***between*** studies (that is, consistency is not met when one study reports an association with peak exposure but not cumulative exposure, while another study reports an association with cumulative exposure but not peak exposure).

Failure to fully integrate evidence in this manner, along with numerous other limitations in EPA's synthesis of the epidemiological evidence, are discussed in detail in the sections that follow. They can be broadly summarized as follows:

- EPA lumps together myeloid leukemias, failing to differentiate between AML and CML, which have very distinct genetics and risk factors.
- EPA fails to truly weigh and integrate the available evidence: it inappropriately downgrades and dismisses important re-analyses and studies, including Checkoway et al. (2015), which are highly informative regarding formaldehyde and LHP malignancies.
- EPA raises up flawed studies such as Hauptmann et al (2009).
- EPA mischaracterizes and overemphasizes risk estimates for purported peak exposure metrics relative to cumulative exposure metrics, which are consistently null.

B. EPA Fails to Differentiate AML and CML Contrary to NASEM's Explicit Recommendation

NASEM (2011) recommended that the EPA synthesize the results for specific LHP cancers. The 2011 NASEM committee that reviewed the 2010 Draft Assessment explicitly recommended that EPA should use the most specific diagnoses when available:

> The committee recommends that EPA focus on the most specific diagnoses available in the epidemiologic data, such as acute myeloblastic leukemia, chronic lymphocytic leukemia, and specific lymphomas.[95]

While it no longer groups "all LHPs," EPA grouped AML and CML under "myeloid leukemia" and then summarized the few results available for AML and CML separately.

In the 2022 Draft Assessment, EPA attempts to justify its use of the broader category of myeloid leukemia by asserting that studies addressing acute and chronic sub-types separately have produced similar results:

> The pattern of increased risk of myeloid leukemia (ICD-8/9: '204') associated with exposure to formaldehyde reflects the associations seen within two subtypes, AML and CML. Among the studies with separate estimates by subtype, risks were elevated for both AML and CML, with the associations for CML appearing to be as strong as or stronger than the associations with AML.[96]

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[95] NASEM 2011 at 11.

[96] 2022 Draft Assessment at 1-443.

1. **AML and CML have very distinctive genetic differences.**

Ninety-five percent of CML cases involve the "Philadelphia (Ph) chromosome" (i.e., reciprocal translocation of genetic material between chromosome 22 and chromosome 9 [t(9;22)(q34;q11)]. AML on the other hand has multiple subtypes and chromosome abnormalities.

> The classification of AML includes 20 definitive and 2 provisional subtypes [5]. AML generally has a rapid onset, often diagnosed due to the development of infections, bleeding, or fatigue that result from pancytopenia, and a variable prognosis, depending upon the molecular genetic profile of the subtype and individual response to therapy. AML is a genetically diverse disease, with 40–55% of patients having chromosome abnormalities that can be identified using conventional analysis techniques [12–14]. The most common genetic change is the loss of genetic material in chromosome 5 or chromosome 7 [13]. Others include deletions in parts of chromosomes (e.g., the long arms of chromosomes 5, 7, and 9), insertion of genetic material, inversions of genetic material (e.g., involving chromosome 16), duplications, and translocations (e.g., t[8;21], t[15;17], and 11q23 translocation]) [13]. Approximately 40–50% of AML patients have a normal karyotype and harbour mutations within specific genes including IDH1, IDH2, FLT3, and NPM1. Some AMLs develop secondary to MDS [myelodysplastic syndromes] and these occur in patients with acquired mutations in genes encoding for myeloid transcription factors (RUNX1, CEBPA) or signal transduction proteins (FLT3) [9]. However, de novo AMLs are also diagnosed in patients with mutations in RUNX1, CEBPA, FLT3 or MLL, but these patients do not have mutations in the genes associated with prior MDS (described above) [9]. Estey (2018) estimated that one-third of patients clinically diagnosed with de novo AML will exhibit genetic mutations specific for secondary AML [9]. AML is more common in the elderly, with more than 58% of cases diagnosed among those 65 years of age or older [10]. (Mundt et al. 2021)[97]

> In CML, the proliferating cells are mature cells of the myeloid lineage, which have differentiated into functional formed elements of the blood. The development of CML involves an acquired cytogenetic abnormality in the pluripotent hematopoietic stem cells (HSCs) or myeloid progenitor cells located in the bone marrow. Ninety-five percent of CML cases involve the reciprocal translocation of genetic material between chromosome 22 and chromosome 9 [t(9;22)(q34;q11)]. This translocation results in an abnormally shortened version of chromosome 22, known as the "Philadelphia (Ph) chromosome" [17, 18]. In the United States, the median age at diagnosis of CML was 65 years, while the median age at death was 77 years. The incidence rate among males, for all races and ethnicities and all age-groups, was 2.4 per 100,000 population, while among females the rate was 1.4 per 100,000. Incidence among white males was 2.5 per 100,000 while the incidence was 2.2 per 100,000 among black males. Incidence among those under 65 years of age was 1.1 per 100,000 population, but nearly seven times higher (i.e., 7.6 per

[97] Mundt KA, Dell LD, Boffetta P, Beckett EM, Lynch HN, Desai VJ, Lin CK, Thompson WJ. The importance of evaluating specific myeloid malignancies in epidemiological studies of environmental carcinogens. BMC Cancer. 2021 Mar 6;21(1):227.

100,000) among those 65 and over. Incidence among the population aged 65 and over was highest among white males (11.1 per 100,000), followed by black males (8.2 per 100,000), white females (5.7 per 100,000) and black females (4.9 per 100,000).[10]. (Mundt et al. 2021)

2. Risk factors differ for AML and CML.

Medline Plus, a website of the National Library of Medicine (NLM), and the American Cancer Society (ACS) list established risk factors for AML and CML. The list for CML is very short as only age, gender and radiation exposure have been conclusively linked to CML. The list of risk factors for AML, however, is comparatively quite long, and includes cigarette smoking and some chemical exposures. Despite this, neither NLM nor ACS site list formaldehyde exposure as an established risk factor for AML.

AML	CML
Medline Plus The factors that raise your risk of AML include: • Being male • Smoking, especially after age 60 • Having had chemotherapy or radiation therapy • Treatment for acute lymphoblastic leukemia (ALL) as a child • Exposure to the chemical benzene • A history of another blood disorder such as myelodysplastic syndrome (https://medlineplus.gov/acutemyeloidleukemia.html)	Medline Plus It is hard to predict who will get CML. There are a few factors that could raise your risk: • Age - your risk goes up as you get older • Gender - CML is slightly more common in men • Exposure to high-dose radiation (https://medlineplus.gov/chronicmyeloidleukemia.html)

American Cancer Society:
There are some known risk factors for acute myeloid leukemia (AML):
• Getting older
• Being male
• Smoking
• Being exposed to certain chemicals
  ○ Benzene
  ○ "Some studies have linked AML risk to heavy workplace exposure to formaldehyde, but this link has not been seen in some other studies."
• Being treated with certain chemotherapy drugs
	American Cancer Society:
	The only risk factors for chronic myeloid leukemia (CML) are:
	• **Radiation exposure**: Being exposed to high-dose radiation (such as being a survivor of an atomic bomb blast or nuclear reactor accident) increases the risk of getting CML
	• **Age**: The risk of getting CML goes up with age
	• **Gender**: This disease is slightly more common in males than females, but it's not known why
	There are no other proven risk factors for CML. The risk of getting CML does not seem to be affected by smoking, diet, exposure to

• Being exposed to radiation • Having certain blood disorders • Having a genetic syndrome • Having a family history of AML (https://www.cancer.org/cancer/acute-myeloid-leukemia/causes-risks-prevention/risk-factors.html)	chemicals, or infections. CML also does not run in families. (https://www.cancer.org/cancer/chronic-myeloid-leukemia/causes-risks-prevention/risk-factors.html)

The difference in risk factors between AML and CML has been reported in the literature evaluating results for studies of formaldehyde workers:

> Although both AML and CML arise in myeloid stem cells, the risk factors associated with AML and CML differ. Most individuals diagnosed with CML have a gene mutation in the leukemia cells called the Philadelphia chromosome, describing the translocation between chromosomes 22 and 9. The translocation leads to the development of the Bcr-Abl oncogene, and this gene instructs the bone marrow to produce Bcr-Abl tyrosine kinase, leading to the development of CML. In addition, the known risk factors for AML—tobacco smoking, exposure to benzene, chemotherapy, or radiation treatment—are not recognized risk factors for CML. High-dose radiation, such as that experienced by survivors of atomic bombs or nuclear reactor accidents, is the only recognized environmental risk factor for CML. These recognized differences in histopathology and in the risk factors for AML and CML raise the question of whether the reported association between formaldehyde exposure and combined MLs reflects an underlying association between formaldehyde exposure and the more plausible specific type of leukemia, AML. (Checkoway et al. 2015).

3. EPA opted not to provide conclusions specific to AML and CML

Several epidemiological studies provided separate results for AML or CML. As demonstrated in Table 2 from Mundt et al. (2021), which was not cited in the 2022 Draft Assessment, there are no statistically significant risk estimates indicating potentially increased risk of myeloid leukemia, AML, or CML in any of the most informative occupational cohort studies on formaldehyde. Given the limited identified risk factors for CML, the alleged finding of "strong" associations of formaldehyde with CML should have raised concerns related to "sensitivity" (and perhaps also plausibility).

Table 2 Formaldehyde exposure and risk of specific types of myeloid malignancy by exposure category

Reference	Exposure Category	Myeloid leukemia			AML			CML		
		No. of cases	Point estimate	95% CI	No. of cases	Point estimate	95% CI	No. of cases	Point estimate	95% CI
Overall Results in Most Informative Cohorts										
Meyers 2013 [29]	Exposed	21	1.28	0.79–1.96	14	1.22	0.67–2.05	5	1.35	0.44–3.15
Coggon 2014 [30]	Exposed	36	1.20	0.84–1.66						
Checkoway 2015 [31]	Exposed	44	0.86	0.64–1.16	30	0.80	0.56–1.14	13	0.97	0.56–1.67
Results of Category at Highest Exposure in Studies										
Beane Freeman 2009 [32]	Peak exposure > 4 ppm	19	1.78	0.87–3.64						
Checkoway 2015 [31]	Peak exposure > 4 ppm	10	1.80	0.85–3.79	6	1.43	0.56–3.63	4	3.07	0.83–11.40
	Cumulative exposure > 2.5 ppm-yrs	14	0.94	0.47–1.86	10	0.96	0.43–2.16	4	0.92	0.25–3.36
Coggon 2014 [30]	High exposure, > one year	50	0.96	0.24–3.82						
Saberi Hosjineh 2013 [33]	≥Low exposure				N/A	1.01	0.65–1.57	N/A	0.92	0.46–1.84
Meyers 2013 [29]	Duration of exposure 10 + yrs.	10	1.84	0.88–3.38	7	1.81	0.73–3.73			
Talibov 2014 [34]	Cumulative exposure > 1.6 ppm-yrs				424	1.17	0.91–1.51			

The 2022 Draft Assessment, however, refers to non-null but imprecisely estimated point estimates in the text, thereby misrepresenting the actual results for CML reported in these studies. For example, EPA writes: "All four studies (Checkoway et al. 2015, Saberi Hosnijeh et al. 2013; Blaier et al. 2001; Stroup et al. 1986) reported elevated risks of CML."[98] However, only Stroup et al. (1986) reported a statistically significantly increased risk for CML (SMR 8.8, 95% CI 1.8 – 25.5) which was very imprecisely estimated as indicated by the wide confidence interval. Checkoway et al. (2013), based on the NCI study data but not reported in Beane Freeman et al. (2009), reported an apparently "elevated" relative risk estimate for CML (which was not statistically significant). It is this three-fold estimate for CML which drives the appearance of an "elevated" risk for all myeloid malignancies combined in the NCI cohort study, as the AML-specific estimate is much lower (and also not statistically significantly increased).

[98] 2022 Draft Assessment at 1-443.

Blair et al. (2001) reported a nearly three-fold elevated risk of CML but it was based on one case (and it was not statistically significant).

Table 2 from Mundt et al. (2021) illustrates that chance cannot be excluded for any of these reported associations. Thus, this is not "robust" evidence of an association. Ultimately, EPA may be correct that myeloid leukemia results are similar to results for AML and CML as a more complete and transparent examination indicates no clear consistent evidence of an excess risk for either of these two myeloid malignancies.

4. EPA relies too heavily on mortality studies

a. Leukemia mortality data have limitations

EPA notes in appendix A of the 2022 Draft Assessment that use of mortality data in the occupational studies on formaldehyde may be an issue:

> For some cancers, the reliance of cohort studies on death certificates to detect cancers with relatively high survival may have underestimated the actual incidence of those cancers, especially when the follow-up time may have been insufficient to capture all cancers that may have been related to exposure. The potential for bias may depend upon the specific survival rates for each cancer. Five-year survival rates vary among the selected cancers (see Table A-100), from 86% for Hodgkin lymphoma (HL) to less than 50% for multiple myeloma (MM), myeloid leukemia (ML), and oro/hypopharyngeal cancer. EPA considered the likelihood of underreporting of incident cases to be higher for mortality-based studies of HL and LL which may result in undercounting of incident cases and underestimates of effect estimates compared to general populations (e.g., Mayr et al., 2010; Hansen and Olsen, 1995; Hansen et al., 1994; Hayes et al., 1990; Solet et al., 1989)."[99]

In table A-100,[100] however, the 5-year survival percentage (2005-2011) for CML was reported as 63.2% and for AML as 25.9%, reflecting a substantial difference. The impact of this difference on the myeloid leukemia epidemiology studies that do not address type of leukemia is unknown.

Formaldehyde studies have noted the limitations of using mortality data for different leukemia subtypes. For example, one study noted that "[i]t is…difficult to disentangle leukemia subtypes using mortality data, since 15–30% of deaths from leukemia in most European countries, including Italy, are of undefined subtype [22]." (Pira et al. 2014).

b. EPA Dismisses the available AML and CML incidence data

The 2022 Draft Assessment essentially dismisses the finding of the two studies that analyzed myeloid cancer incidence data (Saberi Hosnijeh et al. 2013 and Talibov et al. 2014) since both received "low confidence" ratings. The EPIC cohort, the only prospective study with incidence data, identified 49 incident myeloid leukemia cases with formaldehyde exposure as determined by a job exposure matrix. This study method avoids the major problems associated with under-ascertainment of cancers based on death records and uses exposure estimation methods

[99] 2022 Draft Assessment (Appendix) at A-677-A-678.
[100] 2022 Draft Assessment (Appendix) at A-678.

comparable to other more highly rated studies; however, EPA inexplicably downgraded it to the Group C exposure level category. This illustrates again the inconsistent application of EPA's own rating classification guidelines and its resulting unreproducible and therefore questionable study selection (e.g., Hauptmann et al. 2009) and deselection (e.g., Saberi Hosnijeh et al. 2013) decisions. The 2022 Draft Assessment further described the study as not evaluating latency even though the age at recruitment (mean of 57.39; SD of 7.96) for the 201 total myeloid leukemias would have been sufficient to investigate any reasonable latency period relevant to exposure to formaldehyde and covers the age range at which background rates of leukemias are relatively high.

Similarly, Talibov et al. (2014) received an Exposure Group D classification even though the Nordic Occupational Cancer study job exposure matrix (NOCCA-JEM) was used to classify every AML case registered over 15 years in the five Nordic countries. EPA downgraded Talibov et al. due to their use of census data, but Talibov et al. noted that "[i]f there were different occupational codes in census records for a given person, the individual was assumed to have changed occupation in the middle of the known census years." With 136 AML cases with estimated formaldehyde exposure greater than 1.6 ppm-years, this study should have received a higher confidence rating and more weight in the interpretation of the results. Talibov et al. (2014) reported no excess incident (not mortality) risk of AML among workers classified as occupationally exposed to formaldehyde.

c. EPA's over-reliance on mortality is compounded by elevating the results of a case-control analysis of deaths drawn from three proportionate mortality studies (Hauptmann et al. 2009)

The limitations of proportionate mortality studies are well known and primarily derive from the lack of information on the composition of the cohort which is being followed.

> An extreme example of loss to follow-up occurs when one has no accurate data on the composition of the cohort, but one has a set of death records. The proportion of deaths due to each cause arising from a particular cohort is known, but not the absolute mortality rates. One is then led to a study of proportional mortality rates, comparison being made either with the proportions seen in the general population or among subgroups in the study group." (Breslow and Day, 1987, p. 45)[101]

> The approach is formally equivalent to a case-control study based on deaths in which the cases have died from one cause of death and the controls are selected from deaths from all other causes. Seriously biased results can be obtained as for example an apparent strongly protective effect for cigarette smoking against dying from mesothelioma (Blot et al. 1980); but, provided one is aware of the dangers, useful results can be obtained. (Breslow and Day, 1987, p. 46)

[101] Breslow NE, Day NE. Statistical methods in cancer research. Volume II--The design and analysis of cohort studies. IARC Sci Publ. 1987;(82):1-406.

Analyzing death certificates (i.e., a proportionate mortality study) using case-control analysis does not overcome the inherent limitations of non-random sampling of the cases and controls, and may imply a stronger study design (i.e., case-control) than was used.

Furthermore, careful examination of the characteristics of the myeloid leukemia cases and the controls reveals a number of possible issues with interpreting the analyses of Hauptmann et al. (2009). The following differences in characteristics of the two groups are derived from Table 1 in the publication:

Characteristic	Control deaths (n=265)	Myeloid leukemia deaths (n=34)
Year of death before 1976	25% (n=66)	35% (n=12)
Age at death ≤ 66 years	50% (n=132)	39% (n=13)
Age at death >66 years	50% (n=133)	62% (n=21)
Male	92% (n=244)	97% (n=33)
White race	89% (n=235)	100% (n=34)
Ever smoking	78% (n=207)	88% (n=30)
>30 years worked in funeral home	48% (n=128)	61% (n=21)

The ability "to control" for these characteristics within a case-control analysis of death certificates that may inherently reflect selection bias is challenging and, in this particular study, the attempt to control for differences in several characteristics among cases and controls appears insufficient, if even possible. Of particular concern are differences in the percentages between the characteristics "age at death >66 years," "male," and "ever smoking," each of which may influence rates of AML and/or CML. While Hauptmann et al. stated that smoking was not associated with embalming practice, the data suggest otherwise (30 of 34 myeloid leukemias fell into the "ever smoking" characteristic and 33 of 34 myeloid leukemias had a history of embalming). Hauptmann et al. (2009) stated that they performed a sensitivity analysis adjusting for cigarettes smoked per day with similar results, but the better predictor of smoking risk is duration of smoking (or pack-years, which incorporates aspects of both measures).

Nevertheless, even use of smoking duration as a characteristic may not have been able to adequately control for such highly correlated exposures, especially given the lack of adequate proportions of cases and controls that had one but not both of the highly correlated risk factors (i.e., statistical "adjustment" is not capable of deconfounding the analysis). As smoking is an established cause of AML, it is likely that the apparent association between mortality and formaldehyde reflects the correlations with smoking and age. In other words, even attempting to adjust for the potential confounding effect of smoking, the association between formaldehyde exposure and mortality in this study likely remains confounded.

Many of these same concerns and issues have been expressed in the published literature (Cole et al. 2010).

> "In sum, despite some evidence of a formaldehyde–ML association in the embalmers study, there is little evidence of exposure–response relationships. The

effects of the cases' earlier (in calendar time and age) employment are unknown but may have resulted in more embalmings, higher peak exposure, etc. The ever–never control of cigarette smoking may not have been adequate to eliminate the effect of the causal association between smoking and the MLs." (Cole et al. 2010, p. 165)[102]

The PMRs in the three underlying studies of embalmers suggested a weak association between formaldehyde and the MLs. For the embalmers study to add support to that association it would have to provide persuasive evidence of exposure–response relationships for specific exposure indices. The embalmers study concludes that, 'formaldehyde exposures in the funeral industry were associated with statistically significant increased risk for mortality from myeloid leukemia'. The statement rests on two statistically significant trends seen in unreliable data and three stratum-specific risk estimates of borderline statistical significance. In contrast to the quote above, there is no 'increased risk' of ML mortality presented in the embalmers study as the only data provided are relative risk estimates. The PMR of 108 for the MLs, estimated by us, suggests that there is little or no actual, or absolute, increased risk. (Cole et al. 2010, p. 165)

Apart from the fundamental weakness of the PMR study approach, there are several other indicators that the study is susceptible to several significant sources of bias, especially regarding some of the information on which surrogates of formaldehyde exposure were based:

- Peak exposure (as well as average and cumulative exposure) was estimated using a predictive model and information on lifetime embalming work practices. The predictive model was based on industrial hygiene data collected by Stewart et al. (1992) during 25 embalmings at a mortuary school in the early 1990s. The exposure conditions and circumstances (ventilation rate, formaldehyde solution concentration, intact or autopsied body, spills) were varied in the model. There were no industrial hygiene measurements of peak exposure *per se*; however, peak exposure was estimated based on running 15-minute averages from a direct-reading instrument that monitored real-time formaldehyde concentrations during the embalmings.
- Information on lifetime embalming work practices was collected from next-of-kin or co-workers during 1990-1992. However, study subjects (cases and controls) had died during 1960 to 1986, a minimum of 4 years and as many as 32 years earlier than when the interviews with next-of-kin were conducted.
- Differential misclassification of exposure is likely. Next-of-kin of cases who died from leukemia may have recalled exposure history more completely than the next-of-kin of controls, especially if they believed that their loved one's cancer may have been related to exposures in the workplace. Next-of-kin of controls (who died from cardiovascular diseases, strokes, accidents, pneumonia and other non-cancer causes of death) may have

[102] Cole P, Adami HO, Trichopoulos D, Mandel J. Formaldehyde and lymphohematopoietic cancers: a review of two recent studies. Regul Toxicol Pharmacol. 2010 Nov;58(2):161-6.

reported less information because they did not believe that their loved one's death was related to exposures in the workplace.

- Not only are these variables (i.e., number and duration of embalmings per calendar period, frequency of spills per calendar period, embalming of an intact body versus autopsied body) needed to estimate cumulative exposure, these same variables are needed to estimate peak exposure. Further, there is some evidence of differential recall between cases and controls for input parameters into the exposure model. Specially, frequency of spills, duration of embalming an intact corpse, and duration of embalming an autopsied corpse were more likely to be missing from controls subjects than case subjects (43% versus 37%, 43% versus 38%, 45% versus 40%). Controls were more likely than cases to have a single value for these variables (17% versus 11%, 17% versus 11%, 17% versus 13%). Therefore, peak exposure was likely to be substantially misclassified and the direction of the bias could be away from or toward the null.

In summary, the Hauptmann et al. (2009) study appears not to have been fully evaluated for key aspects of study quality, and, objectively, would not contribute to the claimed "robust" evidence of association between formaldehyde exposure and myeloid leukemias.

5. The EPA mischaracterized the findings of the reanalysis of the NCI cohort study by Checkoway et al. (2015) and downgraded the exposure assessment without consideration of the issues with the peak exposure definition in the Beane Freeman et al. (2009) analysis of myeloid leukemia.

The contradictory decision of the 2022 Draft Assessment to downgrade the rating for Checkoway et al. (2015) to low due to their use of a different (albeit more conventional) definition of peak exposure than Beane Freeman et al. (2009), while maintaining a high confidence rating for Beane Freeman et al., appears arbitrary and would be troubling if due to reviewer bias. The table below sets out comparable statements and results from both the Beane Freeman et al. (2009) and Checkoway et al. (2015). Further, Checkoway et al. (2015) incorporated additional analyses not completed by Beane Freeman et al. (2009).

	Beane Freeman, et al. (2009)	**Checkoway et al. (2015)**
Statistical method	Poisson regression	Cox Proportional Hazards
Myeloid Leukemia Results	No excess risk of myeloid leukemia mortality Exposed SMR=0.90 (95% CI: 0.67-1.21; n=44) Nonexposed SMR-0.65 (95% CI: 0.25-1.74; n=4)	No excess risk of myeloid leukemia mortality Exposed SMR=0.86 (95% CI: 0.64-1.16; n=44) Nonexposed SMR-0.69 (95% CI: 0.19-1.76; n=4)
Cumulative exposure and/or	"No statistically significant associations were observed with average intensity (Table 3) or cumulative exposure to	"Myeloid leukemia (all types combined) was not associated with cumulative formaldehyde exposure in the entire cohort. There was, however, a modest, but

average intensity	formaldehyde (Table 4).” (p. 754)	not statistically significant, association of cumulative exposure and ML among workers employed 1 year or more (Table 3).” (p. 788)
Definition of “Peak” exposure	“short-term exposures (generally less than 15 minutes) that exceeded the TWA8 category”.12,21 Workers in jobs not identified as having peak exposure levels that exceeded the TWA8 category were assigned the TWA8 intensity category as their peak exposure. Thus, peaks were defined on a worker-specific relative basis. Moreover, neither frequency nor duration of peaks had been included in the definition of the peak exposure metric previously (e.g., at least 1 year of employment in jobs likely experiencing more than 4 ppm exposure for 15 to 60 minutes at least weekly).” (Source: Checkoway et al. 2015) “Because there was no direct information on frequency of peaks, a higher degree of uncertainty is associated with the frequency than the level of peak exposure.” (Beane Freeman et al. 2009)	Absolute Peak Exposure “we redefined peak exposures on an absolute scale, that is, at least 1 continuous month of employment in jobs identified in the original exposure characterization as likely having short-term exposure excursions of 2 ppm or more to less than 4 ppm or 4 ppm or more on a weekly or daily basis. Our definition of peak exposure did not include employment in jobs likely experiencing (1) short-term excursions more than 0 ppm and less than 2 ppm; (2) short-term excursions identified as occurring as frequently as hourly; and (3) short-term excursions identified as occurring as infrequently as monthly.”
Peak formaldehyde exposure	“Statistically nonsignificant associations were observed for myeloid leukemia (RR = 1.78; 95% CI = 0.87 to 3.64, *P* trend = .13).” (≥ 4 parts per million [ppm] vs >0 to <2.0 ppm)	“Peak exposure of 2.0 ppm or more to less than 4 ppm was associated with ML in the full cohort (HR = 2.09; 95% CI, 1.03 to 4.26) and similarly among those employed 1 year or more (HR = 2.49; 95% CI, 1.01 to 6.15) (Table 4). HRs for peaks of 4.0 ppm or more were weaker, but still elevated, and trends were not statistically significant (i.e., P_{trend} = 0.06 and 0.08, respectively).”
Myeloid Leukemia Outcomes	Reported results for ML	Reported results for ML, AML, and CML

Conclusion	"It is our opinion that the overall pattern of risks seen in this extended follow-up of formaldehyde workers, although not definitive, warrants continued concern. Further studies are needed to evaluate risks of leukemia and lymphatic tumors in other formaldehyde exposed populations and to assess the biological plausibility of a causal association." (p. 760)	"Causal interpretations for the replicated associations with HL and the unanticipated association with CML are uncertain due to the absence of corroborative evidence from other epidemiologic studies of formaldehyde-exposed cohorts. Furthermore, the absence of established pathogenesis mechanisms for HL and CML raises doubt as to whether these observed associations are causal. No other clear associations for peak or cumulative formaldehyde exposures were observed in this cohort for any of the specific LHM, including AML. Although our re-analysis using redefined "peak" exposure detected associations similar to those previously reported with the combined MLs, our new analyses of AML and CML mortality separately suggest that the observed patterns with peak exposure were confined to CML. Furthermore, when taking into account the timing of peak exposure, no increased risk for AML is seen, as only one AML death occurred within 15 years of first, or even last, peak exposure. Sensitivity analyses assuming all the "unspecified" acute leukemia deaths were AMLs did not change these findings." (p. 792-793)

Thus, as well described by both of these publications, the patterns of risk are not definitive for myeloid leukemias and the additional information on AML and CML provided in Checkoway et al. is indicative of a lack of relationship. Checkoway, et al. (2015) should have been classified as high confidence as well and the more specific results for AML and CML should be given appropriate consideration in the interpretation of the epidemiological evidence.

6. There are significant scientific issues with relying on the peak exposure metric from Beane Freeman et al. (2009).

Beane Freeman et al. (2009) found an association between peak exposure and myeloid leukemia. However, there were no short-term industrial hygiene measurements or measurements of peak exposure in the NCI formaldehyde manufacturers and users cohort. Beane-Freeman et al. (2009) relied on peak exposure that was estimated by Stewart et al. (1986). Stewart et al. (1986) defined peak exposure as short-term exposures (generally less than 15 minutes) that exceeded job-specific 8-hour time-weighted average (TWA) exposure estimates. In the absence of actual short-term industrial hygiene measurements, Stewart et al. (1986) assigned peak exposure to jobs

based on a review of tasks associated with the job and a comparison with the 8-hour time-weighted average (TWA). In analyses of mortality in the cohort, NCI investigators used the maximum peak exposure, and substituted the highest time-weighted average (TWA) for peak exposure for workers who had worked in jobs without peak exposures (Stewart et al. 1986; Hauptmann et al. 2004; Beane Freeman 2009).

In a reanalysis of the NCI cohort, Checkoway et al. (2015) reported that there were no associations between peak exposure and acute myeloid leukemia while observing that there were suggestive associations between peak exposure and chronic myeloid leukemia. To address the issue of the misclassification of peak exposure introduced when the NCI investigators mixed workers having a presumed peak exposure (that is, a presumed short-term exposure that exceeded the TWA exposures based on work tasks) with workers in jobs that did not experience peak exposures (that is, workers who did not experience a presumed peak exposures that exceeded the TWA exposures based on work tasks), Checkoway et al. (2015) refined the peak exposure metric and conducted additional analyses. Checkoway et al. (2015) defined peak exposures for workers with at least one continuous month of employment in jobs with peak exposures identified by the exposure assessment investigators (Stewart et al. 1986). Checkoway et al. defined peak exposures as the group likely having short-term exposure excursions of $\geq$2 ppm to <4 ppm or $\geq$4 ppm on a weekly or daily basis (as identified by Stewart et al. 1986). Checkoway et al. (2015) excluded workers who were only exposed to peaks as infrequently as monthly or who were exposed to short-term excursions occurring as frequently as hourly. In the former case, occasional peaks (as infrequent as monthly) are unlikely to have an appreciable effect on cancer risk; in the latter case, excursions that occur on an hourly basis will be reflected in a higher TWA exposure overall for the job. Excursions occurring on an hourly basis are less likely to represent an intermittent peak exposure *per se* and are more likely to reflect constant high-level exposure. This definition of peak exposure explicitly adds a time dimension that was missing from the analysis of peak exposure by Beane Freeman et al. (2009).

7. **There is consistent evidence, however, that the relative risk of myeloid leukemia is not associated with cumulative exposure.**

Three of the four studies judged by the EPA to be high quality or moderate quality evaluated cumulative exposure (or used a surrogate for cumulative exposure) and reported inconsistent results between studies. Cumulative exposure was measured as parts per million-years.

A few examples follow:

- Beane Freeman et al. (2009) reported that cumulative exposure to formaldehyde was not associated with myeloid leukemia. Cumulative exposure is the primary standard exposure metric used to identify excess risks in exposed occupational groups (and alternative exposure metrics may be explored if warranted). A reported association between a novel 'peak' exposure metric in a study demonstrating no increased risk of myeloid leukemia overall would require the interpretation that any exposure that is not a 'peak' exposure is protective against myeloid leukemias.
- Checkoway et al. (2015) reported that AML was not associated with cumulative exposure to formaldehyde. Although the relative risk estimate for CML increased with increasing

cumulative exposure, the risk estimates (hazard ratios) were imprecise as indicated by very wide confidence intervals (likely due to one CML death in the referent category).

- Meyers et al. (2013) did not conduct analyses of cumulative formaldehyde exposure and myeloid leukemia; however, duration of exposure is widely considered a surrogate of cumulative exposure. Meyers et al. (2013) reported that the relative risk estimates of myeloid leukemia increased with duration of exposure in Poisson regression models when duration of exposure was analyzed using categories of exposure; however, the wide confidence intervals in categorical analyses indicated the risk estimates were imprecise. For example, the rate ratio was 6.42 (95% CI 1.40 – 32.2) for workers employed 16 to < 19 years and the rate ratio was 1.71 (95% CI 0.25 – 11.0) for workers employed ≥19 years. In contrast, relative risk estimates from Poisson regression models were not statistically significant when duration of exposure was analyzed directly as a continuous variable or transformed using a square root or natural logarithm in an effort to improve model fit). For example, the rate ratio was 1.04 (95% CI 0.97 – 1.12) per additional year of exposure.
- Coggon et al. (2014) did not conduct analyses of cumulative formaldehyde exposure and myeloid leukemia; however, the authors expressed confidence that the high exposure category corresponded to average exposures of 2 ppm or higher and there was no association between workers exposed to high exposures for one year or longer (OR 0.96, 95% CI 0.24–3.82).
- Hauptmann et al. (2009) did not report an exposure-response association with cumulative exposure and AML.

8. The results of analyses of average intensity of formaldehyde exposure and myeloid leukemia consistently do not show increased relative risks of myeloid leukemia.

Three of the four studies judged by the EPA to be high quality or moderate quality evaluated average intensity of formaldehyde (or evaluated a surrogate for average intensity) and reported inconsistent results between studies:

- Beane Freeman et al. (2009) reported that myeloid leukemia was not associated with average intensity of formaldehyde exposure in continuous or categorical analyses although workers exposed to ≥1 ppm had a non-statistically significantly increased risk.
- Meyers et al. (2013) did not conduct analyses of average exposure and myeloid leukemia. Meyers et al. (2013) reported that average levels of formaldehyde in the garment industry were characterized as 0.3–2.7 ppm among eight US garment plants in 1966 and industry average levels in the 1970s and 1980s were characterized as 0.2–2 ppm as reported by the IARC (2006).[103]
- Coggon et al. (2014) expressed confidence that the high exposure category in their analysis corresponded to average exposures of 2 ppm or higher. Overall, the relative risk

[103] Chemical Agents and Related Occupations. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol. 100F. 2006, 2012. Available at https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Chemical-Agents-And-Related-Occupations-2012.

of myeloid leukemia did not increase with average intensity of exposures, although the odds ratio was non-significantly elevated for those exposed to 2 ppm or higher for less than one year (OR 1.77, 95% CI 0.45–7.03) while there was no increased odds ratio in the group exposed to 2 ppm or higher for one year or longer (OR 0.96, 95% CI 0.24–3.82).

- Hauptmann et al. (2009) reported elevated odds ratios of myeloid leukemia and acute myeloid leukemia for average intensity while embalming; however, the odds ratios (ORs) did not increase with increasing average intensity but were high over each category of exposure. The ORs, which ranged from approximately 2.3 to 2.8 were not statistically significant, but the estimates were imprecise as indicated by wide confidence intervals.

Collectively, the associations between various exposure metrics of formaldehyde exposure (duration of exposure, average intensity or TWA exposure, cumulative exposure, or peak exposure) and myeloid leukemia, acute myeloid leukemia or chronic myeloid leukemia are not consistent between studies. The lack of any discernible pattern with exposure metric suggests that the reported associations are likely due to chance.

C. There is No Established Plausible Mode of Action for Myeloid Leukemias

1. EPA continues to rely on flawed studies purportedly demonstrating an MOA.

Despite conceding in the 2022 Draft Assessment that formaldehyde is not systemically distributed, EPA continues to discuss potential, but not scientifically validated MOAs. At the same time, in some parts of the 2022 Draft Assessment, EPA acknowledges the weakness of the MOA body of the evidence. EPA states:

> Generally, evidence supporting the development of LHP cancers after formaldehyde inhalation has not been observed in experimental animals (i.e., rodents), including a well-conducted, chronic cancer bioassay in two species, a similar lack of increased leukemias in a second rat bioassay, and multiple mechanistic evaluations of relevant biological changes, including genotoxicity (i.e., inadequate evidence). **The exact mechanism(s) leading to cancer formation outside of the respiratory tract are unknown.**[104]

EPA supports its causal conclusion regarding LHMs "based on multiple epidemiologic studies that found associations with different exposure metrics, and which were **supported by mechanistic studies in exposed humans that provided biological support for genotoxic and immunologic changes in peripheral blood cells**." (emphasis added).[105]

EPA references Zhang et al. (2010) (as well as an update of the same cohort using the same data; Lan et al. 2015) which "reported effects on myeloid progenitor cells cultured from peripheral blood of exposed workers compared to cells cultured from controls without occupational

[104] 2022 Draft Assessment at lv.
[105] 2022 Draft Assessment (Appendix) at D-30.

formaldehyde exposure." [106] EPA states that "[n]o information is available to determine if either progenitor cell type would be more or less susceptible to formaldehyde-induced genotoxicity."[107]

Interestingly, up until Zhang et al. (2010) was published, formaldehyde had not been reported to induce leukemia-specific chromosomal alterations in human blood stem or progenitor cells (Zhang et al. 2010). In fact, Zhang et al.'s (and by proxy EPA's) hypotheses related to the ability of formaldehyde to damage circulating cells that could reach the bone marrow had all but been disproven in a previous publication by McKinney-Freeman & Goodnell (2004). McKinney-Freeman demonstrated that the normal human peripheral blood repopulating (stem) cells "are vanishingly rare and are not measurable;" thus there remains no evidence that circulating hematopoietic stem cells return to bone marrow during homeostasis (McKinner-Freeman & Goodnell 2004). Additionally, circulating repopulating cells in humans are end stage cells, making the biological plausibility of the mechanisms proposed by Zhang et al. 2010 and adopted by EPA extremely unlikely (Gentry et al. 2013).

In fact, the evidence presented by Zhang et al. (2010) may actually demonstrate an overall *lack* of evidence of a direct genotoxic MOA within bone marrow as formaldehyde does not form either DNA-protein crosslinks (Casanova-Schmitz et al., 1984; Heck & Casanova, 2004) or DNA adducts (Lu et al., 2010) in bone marrow. Therefore, there remains no biological evidence or empirical data to support that the hypothesized mechanisms by Zhang et al. (2009, 2010) (on which EPA's judgements heavily rely) actually occur following inhalation of formaldehyde in humans.

Furthermore, a direct genotoxic effect on the bone marrow, resulting in an impact on circulating cells, has been all but disproved by several studies published *after* Zhang et al.'s (2010) initial study including Lu et al. 2011, Moeller et al. 2011, Yu et al. 2015, and Lai et al. 2016. These studies show that due to the reactive nature of formaldehyde, exogenous formaldehyde is not able to move beyond "the portal of entry" (Mundt et al. 2017).

Furthermore, there is ample literature examining whether formaldehyde might cause mutations leading to cancer in blood progenitor cells. Drs. Albertini and Kaden note in their comment on the 2022 Draft Assessment that EPA failed to include two of their papers:

- Albertini RJ, Kaden DA. 2016. Do chromosome changes in blood cells implicate formaldehyde as a leukemogen? Critical Reviews in Toxicology, 47(2): 145-184.
- Albertini RJ, Kaden DA. 2020. Mutagenicity monitoring in humans: global versus specific origin of mutations. Mutation Research/Reviews in Mutation Research, 786: 108341.

These papers are very relevant to the USEPA conclusion that formaldehyde can cause myeloid leukemia, and speaks to the role, if any, of formaldehyde-induced genotoxicity. The EPA cites evidence of elevated frequencies of chromosomal aberrations or micronuclei in peripheral blood lymphocytes (PBLs) of workers exposed to formaldehyde and concludes that this implicates

[106] 2022 Draft Assessment at 1-520.
[107] 2022 Draft Assessment at 1-520.

formaldehyde as a leukemogen.[108] However, in their comments on the 2022 Draft Assessment, Drs. Albertini and Kaden (EPA-HQ-ORD-2010-0396) state that "There is no implication of causation in these association studies. The association may simply be due to host susceptibility to developing chromosome aberrations, even those that occur spontaneously. This is consistent with mechanisms of cancer development, in which chromosomal-level mutational changes are important key events in cancer induction."

Drs. Albertini and Kaden also point out that in vivo mutation monitoring in PBLs in adults does not implicate the bone marrow in their genesis in normal adults. Only studies using cells such as reticulocytes would allow an informative evaluation of potential formaldehyde-induced chromosome mutations in bone marrow cells – the target tissue. EPA's conclusions about the role of genotoxicity in leukemias are therefore based on a misinterpretation of the genotoxicity data.

2. EPA's speculations on potential MOAs for myeloid leukemia lack evidence and therefore biological plausibility.

The best available science does not provide support for any mechanism or mode of action by which myeloid leukemia may result from inhalation exposure to formaldehyde. Rather, the best available science provides evidence of a lack of biological plausibility of this causal association.

In the 2011 NASEM review of the previous 2010 Draft Assessment, NASEM acknowledged that the causal conclusions regarding the potential for leukemia were largely based on a few selected studies in the epidemiological literature, with little consideration of other streams of evidence such as animal bioassays, dosimetry, or mode of action (MOA) studies. The current 2022 Draft Assessment relies upon many of the same epidemiological studies and gives little consideration to recent epidemiological and mechanistic evidence that provides strong support for the lack of biological plausibility that formaldehyde inhalation exposure is associated with the development of myeloid leukemia.

Despite providing a discussion of LHP cancer biology in the 2022 Draft Assessment (Section 1.3.3) and the biological processes that could be involved in the development of leukemias, no discussion of any potential MOA or mechanisms by which LHP may arise by a direct impact on these biological processes is proposed. EPA also notes the conclusions by European scientific bodies (SCOEL 2017[109]; ECHA 2012[110]) that the observations of associations between formaldehyde exposure and lymphohematopoietic (LHP) cancers are not biologically plausible since formaldehyde is not distributed to distal tissues preventing direct interactions with the bone marrow but ignores these conclusions in the integration of evidence on mode of action and causal associations.

Comments provided by federal agencies during the truncated "scientific consultation" step of the 7-step IRIS process, challenge EPA's conclusions regarding the biological plausibility of an

[108] 2022 Draft Assessment at 1-523-1-524.
[109] SCOEL (Scientific Committee on Occupational Exposure Limits). (2017). SCOEL/REC/125 formaldehyde: recommendation from the scientific committee on occupational exposure limits.
[110] ECHA (European Chemicals Agency). (2012). Committee for risk assessment. RAC. Opinion proposing harmonized classification and labeling at EU level of formaldehyde.

association between formaldehyde exposure and LHPs (https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=353316). Specifically, comments from the Agency for Toxic Substances and Disease Registry (ATSDR) indicate that the lack of mechanistic data explaining an association between health effects and formaldehyde exposure is significant and should be a reason to downgrade the evidence findings:

> 'Evidence indicates' is too strong of a category especially since it appears to be used when there is not mechanistic evidence.[111]

The Office of Management and Budget (OMB) also provided specific comments on this conclusion, noting:[112]

> …we are concerned with EPA's judgement of "evidence demonstrates" for myeloid leukemia. Given the inconsistencies in the epidemiologic data and the lack of proposed MOA, it is not clear that this determination is, as EPA indicates (Overview, page 4), based on "robust human evidence of increased risk in groups exposed to occupational formaldehyde levels, and robust animal evidence of nasal cancers in rats and mice that exhibits steeply increasing incidence at high formaldehyde levels. Strong mechanistic support is provided across species (primarily rats, but also mice, monkeys, and humans), including genotoxicity, epithelial damage or remodeling, and cellular proliferation that are consistent with neoplastic development in a regional, temporal, and dose-related fashion." Claiming "evidence demonstrates" while the confidence in the unit risk estimate is low and the data are limited may result in an overly conservative appreciation of the degree of hazard for myeloid leukemia, particularly considering no MOA has been established to explain how formaldehyde inhalation can cause myeloid leukemia, a disease that results from systemic exposure. The mechanistic information considered by EPA may support associations with local, route-of-exposure, tumors associated with epithelial cells, but does not support the tumorigenesis or carcinogenesis of disease related to systemic exposures.

Although EPA has suggested other indirect modes of action (e.g., oxidative stress), the 2022 Draft Assessment explicitly acknowledges the lack of evidence to support any indirect mode of action for formaldehyde exposure to cause myeloid leukemia. "Due to the paucity of pertinent mechanistic information, no single, stochastic MOA was identified for LHP cancers associated with formaldehyde exposure."[113]

A proposed MOA related to oxidative stress would implicate other chemicals that cause oxidative stress; however, there are many examples of chemicals that cause oxidative stress but do not cause myeloid leukemia. Further, the only evidence of elevated indicators of

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[111] Agency for Toxic Substances and Disease Registry (ATSDR), Comments on the Interagency Science Consultation Draft IRIS Assessment of Formaldehyde–Inhalation dated December 2021 at 3 (Jan. 5, 2022) available at https://ordspub.epa.gov/ords/eims/eimscomm.getfile?p_download_id=544465 [hereinafter ATSDR Comments].

[112] https://ordspub.epa.gov/ords/eims/eimscomm.getfile?p_download_id=544467.

[113] 2022 Draft Assessment at 1-538.

formaldehyde-induced oxidative stress and inflammation in the bone marrow presented by EPA are studies conducted in mice in which the animals were co-exposed to methanol (Yu et al. 2014; Ye et al. 2013). Because of this co-exposure, EPA appropriately notes that this draws into question the validity of these findings.

EPA acknowledges that decades of dosimetry research indicate that inhalation of formaldehyde does not result in elevation of formaldehyde levels naturally present in the blood. Therefore, in drawing any conclusions regarding the potential for formaldehyde to cause leukemia or developing any postulated MOA to explain how this could occur, it is important to understand the relative dosimetry of exogenous and endogenous formaldehyde exposures. However, even though EPA acknowledges the toxicokinetics and biological processes that would be involved that are relevant to the potential development of myeloid leukemia following inhalation exposure to formaldehyde, they ignore the best available science in concluding:

> While mechanisms for the induction of myeloid leukemia are yet to be elucidated, they do not appear to require direct interactions between formaldehyde and bone marrow constituents, and either are different in animals or the existing animal models tested thus far do not characterize the complex process leading to cancers in exposed humans.[114]

So rather than draw conclusions based on the best available science, EPA speculates that some unknown mechanism may be involved.

3. EPA fails to consider Gentry et al. (2020) in assessing the biological plausibility of a causal association between inhalation of formaldehyde and myeloid leukemia

Since the 2010 Draft Assessment, Gentry et al. (2020)[115] evaluated postulated MOAs for myeloid leukemia following inhalation exposure to formaldehyde applying the World Health Organization (WHO)/ International Programme on Chemical Safety (IPCS) MOA framework (Meek et al. 2014).[116] While a similar publication with the application of this guidance to the MOAs for portal of entry effects following inhalation exposure to formaldehyde (McGregor et al. 2006)[117] has been included in the 2022 Draft Assessment, the Gentry et al. (2020) publication was not cited or considered.

As described in Gentry et al. (2020), there have been four postulated MOAs for the development of myeloid leukemia following inhalation exposure to formaldehyde. Common to each of the four postulated MOAs is the ability of formaldehyde to produce direct DNA-reactive mutagenic

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[114] 2022 Draft Assessment at 1-542.

[115] Gentry, R, Thompson, CM, Franzen, A, Salley, J, Albertini, R, Lu, K, Green, T (2020) Using mechanistic information to support evidence integration and synthesis: a case study with inhaled formaldehyde and leukemia. Critical Reviews in Toxicology 50(10): 885-918.

[116] Meek ME, Boobis A, Cote I, Dellarco V, Fotakis G, Munn S, Seed J, Vickers C. (2014) New developmental in the evaluation and application of the WHO/IPCS framework on mode of action/species concordance analysis. J Appl Toxicol. 34(1):1-18/

[117] McGregor D, Bolt H, Cogliano V, Richter-Reichhelm HB (2006) Formaldehyde and glutaraldehyde and nasal cytotoxicity: Case study within the context of the 2006 IPCS Human Framework for the Analysis of a cancer mode of action for humans. Crit Rev Toxicol 36:821-835.

damage. Formaldehyde *in vitro* has clearly been shown to have genotoxic potential (e.g., SCEs, micronuclei) in all systems tested ranging from plasmids and bacteria to mammalian cell cultures; however, differences have been reported in the genotoxicity literature for *in vivo* systems (Albertini and Kaden 2017). Notably, studies that have attempted to measure genotoxicity (micronuclei) in human volunteers exposed to formaldehyde by inhalation in controlled settings reported no changes in genotoxic endpoints in buccal cells (Speit et al. 2007) or peripheral blood cells and nasal epithelial cells (Zeller et al. 2011). The 2022 Draft Assessment incorrectly reported these studies (Speit et al. 2007; Zeller et al. 2011) to have equivocal results.

The study authors (Speit et al. 2007; Zeller et al. 2011) concluded that under the conditions of these studies (at constant concentrations up to 0.7 ppm 4 hours/day for five days or 0.4 ppm plus four peaks of 0.8 ppm for 15 minutes), inhalation of formaldehyde did not lead to genotoxic effects in peripheral blood cells or the nasal mucosa. Gentry et al. (2020) applied the WHO/IPCS MOA Framework, which provides a structured framework for evidence integration, using modified Bradford Hill criteria to aid in determining the biological plausibility of causality. Gentry et al. (2020) concluded that all the available evidence clearly highlights the limited amount of data that support any of the postulated MOAs. Instead, the available evidence supports the null hypothesis that there is no causal association between formaldehyde inhalation exposure and leukemia.

In her comments on the 2022 Draft Assessment (EPA-HQ-ORD-2010-0396), Dr. Gentry notes that the study by McGregor et al. (2006) was included in the section entitled "Mode of action evidence integration and summary of analysis" regarding the potential modes of action for tumors at the portal of entry. This publication provides the results of the application of the 2006 IPCS human framework for the analysis of cancer mode of action (MOA) for formaldehyde, considering the available postulated mode of action.

Despite the inclusion of McGregor et al. (2006), Gentry et al. (2020), a similar publication, was not included, even though EPA was made aware of the results of Gentry et al. (2020) on several occasions. In addition to the publication, Gentry et al.'s work was presented at multiple scientific meetings (in which Dr. Gentry interacted with EPA scientists regarding these results) as well as at a webinar for EPA scientists on June 17, 2020.

The science presented in Gentry et al. (2020) is critical to examining the potential biological plausibility of a causal association between inhalation of formaldehyde and myeloid leukemia and should have been referenced and integrated into the 2022 Draft Assessment.

D. EPA Mistakenly Assumes that Biomarkers of exposure (or even effect) in circulating blood cells are the same as genotoxicity in target cells.

When discussing genotoxicity, "biomarkers" may refer to biomarkers of exposure or biomarkers of effect. For example, DNA adducts, protein adducts, and DNA-protein adducts are biomarkers of exposure; mutations, which are heritable structural or numerical alterations in the DNA which permanently and irreversibly alter genetic information in the call, are biomarkers of effect;

metabolic polymorphisms may represent biomarkers of susceptibility; other biomarkers may fall between these two extremes.

When discussing genotoxicity results, it is important to differentiate those which reflect actual genetic changes, from those that indicate exposure or even DNA damage, but which do not indicate mutations have occurred. Comet (single cell gel electrophoresis) assay results indicate DNA damage. Micronucleus assay results indicate DNA damage in vivo, although the assay may manifest chromosomal changes while cells are cultured in vitro. The figure below (National Academies of Science, 2006, Human Biomonitoring for Environmental Chemicals) illustrates how this is not a simple delineation of exposure (formaldehyde) to effect (heritable changes) but instead reflects a continuum on the pathway to disease.

Furthermore, these changes measured in circulating blood cells are only surrogates for the critical cells for health effects–the stem cells or hematopoietic progenitor cells (HPCs) located in the bone marrow. Yet the EPA treats these biomarkers as the equivalent to HPCs, despite the fact that circulating blood cells do not repopulate the bone marrow.

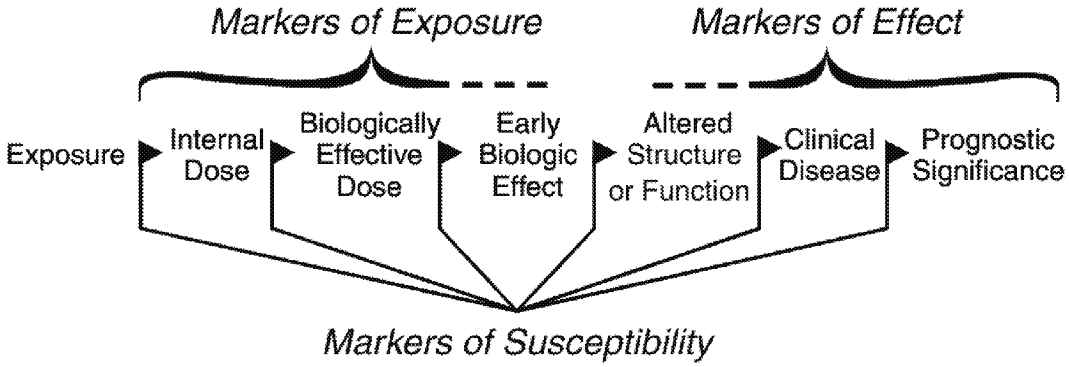

FIGURE 1-1 Simplified flow chart of classes of biomarkers. Source: NRC 1987.

IV. Nasopharyngeal Cancers (NPC)

A. EPA Grossly Misinterpreted the Work of Dr. Marsh, which the 2022 Draft Assessment Cites Throughout

Dr. Marsh's comment on the 2022 Draft Assessment (EPA-HQ-ORD-2010-0396) notes that, although he has published 18 formaldehyde manuscripts, only 10 were cited in the 2022 Draft Assessment. Several of the omitted papers were critical contributions to the literature on the potential human health effects of formaldehyde.

Of the Marsh et al. papers that were not cited in the 2022 Draft Assessment, EPA omitted the following important studies:

- A paper relaying the proceedings of a 2017 formaldehyde risk-related workshop that included 24 invited experts in epidemiology, toxicology, evidence integration and risk

evaluation (Marsh et al. 2019).[118] The workshop conclusions did not support the overall conclusion of the 2022 Draft Assessment regarding the epidemiological evidence for an association between formaldehyde and NPC or leukemia.

- A paper describing the methodological limitations of the NCI formaldehyde cohort study that weighed heavily in the conclusions reached by EPA in the 2010 Draft Assessment (Marsh et al. 2014).[119] Marsh et al. (2014) concluded that the link between formaldehyde exposure and NPC suggested by NCI based on its most recent update of the formaldehyde cohort study is "neither consistent with the available data from the most recent update nor with other research findings from that cohort, other large cohort studies and a series of publications by some of the current authors including an independent study of one of the NCI study plants."
- A reevaluation of mortality risks from leukemia in the NCI formaldehyde cohort study (Marsh and Youk 2004).[120] The authors concluded: "Our reanalysis provided little evidence to support NCI's suggestion of a causal association between formaldehyde exposure and mortality from leukemia and myeloid leukemia… Our finding that NCI's suggestion of a causal association is not robust with respect to alternative categorizations of formaldehyde exposure and methods of data analysis casts considerable additional uncertainty regarding the validity of this suggested association."

The 2022 Draft Assessment also misinterprets and misrepresents several of the Marsh et al. papers that it cites. Of the Marsh et al. studies cited by EPA, the findings of five of these studies were seriously misinterpreted by the agency. These studies include: Marsh et al. (1996), Marsh et al. (2007b), Marsh and Youk (2005), Marsh et al. (2007), Marsh et al. (2016), and Marsh et al. (2002). These misinterpretations arose because EPA either disregarded key findings presented by these studies (as in Marsh et al. (2007b), or improperly extended the results (as in Marsh et al. 1996).

EPA should review all 18 publications and update the 2022 Draft Assessment to include missing studies, correct citation errors, and ensure that the studies are properly characterized and integrated.

B. A threshold dose-response exists for NPC.

Animal evidence clearly demonstrate a threshold for induction of squamous cell carcinoma, which corresponds to concentrations above where cell proliferation is induced (Monticello et al.

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[118] Andersen, M.E., P.R. Gentry, J.A. Swenberg, K.A., Mundt, K.W. White, C. Thompson, J. Bus, J.H. Sherman, H. Greim, H.Bolt, G.M. Marsh, H. Checkoway, D. Coggon, and H.J. Clewell. 2019. Consideration for refining the risk assessment process for formaldehyde. Reg Tox Pharm. 106:210-223.

[119] Marsh, GM, P Morfeld, JJ Collins, and JM Symons. 2014. Issues of methods and interpretation in the National Cancer Institute formaldehyde cohort study. J Occup Med Toxicol 9:22.

[120] Marsh, GM, and AO Youk. 2004. Reevaluation of mortality risks from leukemia in the formaldehyde cohort study of the National Cancer Institute. Regul Toxicol Pharmacol 40(2):113-124.

1991; Connolly et al. 2002 as cited in BfR 2006; Swenberg et al. 1980; Kerns et al. 1983; Monticello et al. 1996).

Other authoritative bodies agree with this assessment. For example:

> It is agreed in accordance with the RAC conclusion on FA carcinogenicity (2012) that experimental results and mechanistic data support "the existence of a threshold type dose-response for induction of nasal tumours, with regenerative cell proliferation being the predominant feature in the carcinogenic process. The genotoxicity of formaldehyde is also expected to play a role above this threshold." However RAC further reflected the uncertainties that "the data does not allow a firm conclusion on a threshold-mode of action or the identification of a threshold", while SCOEL (2016) considered that "the apparent NOAEC of 1 ppm [1.24 mg/m^3] can be considered a mode-of-action based NOAEC for carcinogenic effects at the portal-of-entry" (SCOEL 2016). In line with the Dossier Submitter (DS) RAC concludes that formaldehyde is a locally acting genotoxic carcinogen for which a mode-of-action based limit value for its carcinogenic effect in the nose is very likely. Whether the WHO threshold value of 0.1 mg/m^3 can be considered sufficiently conservative for formaldehyde risk assessment is It is agreed in accordance discussed in the next section."
> — ECHA RAC 2020

> In essence, new experimental data, reported since 2008, clearly indicate that systemic genotoxic action of inhaled [Formaldehyde] FA is not likely, even at exposure concentrations leading to nasal malignancies in the rat.
> — SCOEL 2016

C. EPA failed to consider Thompson et al. (2020), which provides important data integration related to the MOA for formaldehyde-induced nasal tumors.

In Dr. Chad Thompson's comments (EPA-HQ-ORD-2010-0396) on the 2022 Draft Assessment, he notes the absence of his publication (Thompson et al. 2020) that provides important data integration related to the MOA for formaldehyde-induced nasal tumors that USEPA failed to consider. He also identifies several additional publications related to MOA for formaldehyde cancers that were not included in the 2022 Draft IRIS Assessment, including two highly relevant data streams (studies evaluating alcohol dehydrogenase-5 (ADH) and endogenous/exogenous DNA adducts) that USEPA failed to integrate into their MOA analysis for portal of entry cancers.

Dr. Thompson discusses EPA's lack of application of a framework or guidance for conducting an MOA analysis. While EPA discusses isolated events consistent with the 10 key characteristics of carcinogens approach (Smith et al. 2016; Hanahan and Weinberg 2011), without some attempt to place the key events into an ordered se sequence, derivation of toxicity values based on key events occurring before tumor formation becomes increasingly difficult as there is less ability to identify exposure levels that would not likely

progress to cancer. This approach is also in conflict with the 2005 EPA Cancer Guidelines, which specify the use of BBDR models when available, as these models are constructed on critical sub-models that relate exposure to an initiating event that subsequently has a relationship to another key event in a sequence of key events leading to a specific tumor of interest.

1. EPA misinterprets Recio et al. (1992) to support an implausible genotoxic mode-of-action for carcinogenicity.

In his comments on the 2022 Draft Assessment (EPA-HQ-ORD-2010-0396), Dr. Recio notes that EPA incorrectly interpreted a 1992 manuscript on which he was the senior author[121] to support EPA's conclusion about formaldehyde acting through a genotoxic mechanism to induce cancer.[122] Dr. Recio's study examined changes in the p53 tumor suppressor gene (also known as TP53) in squamous cell carcinomas (SCC) from formaldehyde exposed rats. Results showed that 5 of 11 of the rat nasal tumors analyzed had a point mutation in the coding region of p53. EPA concludes that the p53 mutations in rat SCCs implicate these changes in the cancer process. In his comments, however, Dr. Recio points out that EPA's interpretation of his study is wrong. Contrary to EPA's assertions, there are no data to support a role for p53 in formaldehyde-induced neoplasia. Instead, he states that these mutations are **late occurring** "passenger mutations" resulting from known genome instability that occurs in cancers and do not support a mutagenic mode-of-action for tumor outcomes from formaldehyde exposed rats.

D. EPA's Approach to the Evaluation of BBDR Modeling in the 2022 Draft Assessment was Misguided and Inconsistent with EPA's Own Cancer Guidelines

In Dr. Rory Conolly's comments on the 2022 Draft Assessment (EPA-HQ-ORD-2010-0396), he criticizes EPA's approach to the evaluation of the BBDR modeling and EPA's subsequent conclusion that the modeling is too uncertain to support risk assessment. Specifically, Dr. Conolly notes EPA's limited understanding of the CIIT BBDR model and notes that EPA fails to understand that no model is perfect, and that model analysis and iterative refinement support reductions in model uncertainty. He further argues that the model is of sufficient quality to avoid introducing uncertainty due to technical insufficiency, as the 2022 Draft Assessment claims.

Dr. Conolly addresses multiple issues with the BBDR model identified by the USEPA in the 2022 Draft Assessment. He also states that it would have been interesting and informative, and consistent with their own Guidelines for Carcinogen Risk Assessment (EPA, 2005) (which clearly state a default preference for data-driven risk assessment), if EPA had chosen to use its analyses to develop a refined version of the CIIT model. Instead, EPA has rejected the CIIT BBDR model and turned to more empirical approaches. In making this choice, EPA is effectively saying that relevant mechanistic data are confusing and increase rather the decrease uncertainty, a position that is inconsistent with the 2005 guidelines.

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[121] Leslie Recio, Susan Sisk, Linda Pluta, Edilberto Bermudez, Elizabeth A. Gross, Zhuchu Chen, Kevin Morgan, Cheryl Walker (1992) p53 Mutations in Formaldehyde-induced Nasal Squamous Cell Carcinomas in Rats. *Cancer Res* 52 (21): 6113-6116.

[122] 2022 Draft Assessment at 1-319-1-320.

Dr. Conolly concludes that EPA should consider the uncertainties of the BBDR model relative to the hidden uncertainties embedded in the empirical dose-response functions that they prefer, since lack of explicit description of mechanism does not avoid accountability for the mechanism, especially when so much relevant data are available.

In a separate submission, Dr. Thomas Starr also provides comments (EPA-HQ-ORD-2010-0396) related to a novel "bottom up" approach to bounding human cancer risks from chronic inhalation exposure to formaldehyde he developed with Dr. James A. Swenberg. Results from this evaluation are important in bounding the potential risks for cancer in consideration of the endogenous production of formaldehyde. Dr. Starr responds to issues with the "bottom up" approach identified in the 2022 Draft IRIS Assessment and discusses several publications related to this approach that EPA failed to include, calling into question the EPA's systematic review.

A. The Weight of Evidence Does Not Support the Derivation of IURs for Either Myeloid Leukemia or NPC.

The 2022 Draft Assessment indicates that epidemiological data are preferred for dose-response analysis and derivation of toxicity values. In many cases, the epidemiological evidence is not suitable for use in quantitative dose-response due to insufficient exposure-response information or other issues. For formaldehyde, only animal data are adequate to describe the dose-response (i.e., threshold or 'hockey-stick') relationship between formaldehyde and cancer, and these are limited to nasal cancer.

Regarding LHPs, the 2022 Draft Assessment acknowledges that the evidence for these malignancies is of "low confidence," and yet EPA derived an Inhalation Unit Risk (IUR) nonetheless. For specific leukemias (or other specific LHM), neither the animal toxicology nor the epidemiological evidence demonstrates a clear causal relationship and therefore deriving a slope factor or unit risk for leukemia is inappropriate.

With regard to nasal tumors, as discussed in these comments, there is substantive evidence indicating these tumors are the result of cytotoxicity and regenerative proliferation. In its derivation of IURs based on animal data, EPA presented an analysis of potential threshold-like effects (i.e., an RfC based on cellular proliferation). Ultimately, however, EPA concluded that because the formaldehyde-induced tumors could not solely be attributed to cell proliferation and that the evidence "at least in part" supported a mutagenic MOA and a linear no-threshold approach. Importantly, the existence of multiple MOAs does not preclude EPA from deriving toxicity values based on threshold-like responses. In the case of formaldehyde, if genotoxicity were to occur, it is expected only above those exposures associated with regenerative cell proliferation, as noted by the ECHA RAC Committee (2020)[123]:

> It is agreed in accordance with the RAC conclusion on FA carcinogenicity (2012) that experimental results and mechanistic data support "the existence of a threshold

[123] ECHA Committee for Risk Assessment (RAC). 2020. Opinion on an Annex XV Dossier Proposing Restrictions on Formaldehyde and Formaldehyde Releasers.

> type dose-response for induction of nasal tumours, with regenerative cell proliferation being the predominant feature in the carcinogenic process. The genotoxicity of formaldehyde is also expected to play a role above this threshold." However RAC further reflected the uncertainties that "the data does not allow a firm conclusion on a threshold-mode of action or the identification of a threshold", while SCOEL (2016) considered that "the apparent NOAEC of 1 ppm [1.24 mg/m³] can be considered a mode-of-action based NOAEC for carcinogenic effects at the portal-of-entry" (SCOEL 2016). In line with the DS RAC concludes that formaldehyde is a locally acting genotoxic carcinogen for which a mode-of-action based limit value for its carcinogenic effect in the nose is very likely."
> — ECHA RAC 2020

Given the robust scientific evidence that the non-genotoxic MOA predominates and would be protective of any other MOA for carcinogenicity, EPA should assess formaldehyde nasal cancer potency using a threshold (reference concentration (RfC) or no observable adverse effect concentration ("NOAEC")) approach, rather than a linear, no-threshold IUR.

V. Noncancer Health Endpoints: Portal of Entry Effects

A. EPA does not apply a weight of evidence approach in assessing sensory irritation.

The 2022 Draft Assessment discusses sensory irritation as one of the endpoints for acute inhalation exposures and concludes:

> …Overall, the evidence demonstrates that inhalation of formaldehyde causes sensory irritation in humans, given appropriate exposure circumstances. The primary support for this conclusion is based on well-conducted residential studies with mean formaldehyde concentrations >0.05 mg/m^3 (range 0.01 to approximately 1.0 mg/m^3) and controlled human exposure studies testing responses to concentrations 0.1 mg/m^3 and above (Table 1-4).[124]

The 2022 Draft Assessment gives equal weight to *all* the study designs, and simply attributes the variation seen as part of human variability. EPA does not appear to acknowledge that subjective measures can easily be influenced by other factors such as odor perception (Cometto-Muñiz and Cain 1991; Brüning et al., 2014). Six studies were considered for derivation of Points of Departure (PODs) (Hanrahan et al., 1984; Kulle et al 1987; Anderson and Molhave 1983; Liu et al, 1991; Mueller et al., 2013; Lang et al 2008), but only three (Andersen and Molhave, 1983; Hanrahan et al., 1984; Kulle et al 1987 –all medium quality as assessed by EPA, where Andersen and Molhave 1983 was a chapter as opposed to a peer-reviewed publication) were considered for POD derivation in spite of higher quality studies (Lang et al., 2008; Mueller et al., 2013) being available. (Lui et al 1991 was also considered medium quality.)

EPA's rationale for its decision was the following: "An exposure-response trend was not observed for either endpoint. Difficult to define an adverse response level cutoff for these

[124] 2022 Draft Assessment at 1-33.

endpoints" for Mueller et al., 2013; "Difficult to define an adverse response level cutoff for these endpoints and appeared to less sensitive than symptom score" for Lang et al., 2008. However, given the stronger quality of these studies, RfCs could have been derived from NOELs.[125]

B. EPA Inappropriately Dismisses Carefully Designed Chamber Studies

In previous comments on the 2010 Draft Assessment, the 2011 NASEM stated:

> The committee found that EPA dismissed the results of the exposure chamber and other nonresidential studies too readily. Although the exposure durations for the chamber studies are short relative to the chronic duration of the RfC, the studies provide complimentary information that could be used for deriving a candidate RfC.[126]

In response, EPA stated:

> EPA agrees that the controlled human exposure studies provide complementary information and integrated this evidence in concert with those of the occupational and residential studies. In accordance with the criteria for selecting studies for the derivation of candidate RfCs (see Section 2.1.1), EPA uses the dose-response information from epidemiology studies of residential exposure because studies of good quality are available (Liu et al., 1991; Hanrahan et al., 1984) and compares these to cRfCs derived from medium confidence controlled human exposure studies (Kulle, 1993; Andersen and Molhave, 1983).[127]

In other words, EPA agrees with NASEM's comments, but nevertheless creates a new reason to discount the Lang et al. (2008) and Muller et al. (2013) studies.

NASEM and ACC are not alone in noting this shortcoming. In their comments on the 2022 Draft Assessment, Drs. Kaden and Wolkoff expressed concern that EPA's evaluation of noncancer endpoints in the 2022 Draft Assessment ignored several important studies that the WHO 2010 formaldehyde working group, as endorsed by peer reviewers and members of other working groups considered key were ignored. These studies were also considered key in as well as in other publications by Drs. Wolkoff and Nielsen.[128,129] They stated that these key studies – the chamber studies of Lang et al. (2008)[130] and Mueller et al. (2013) – comprise the best available science for deriving a safe exposure concentration for humans. Instead, EPA used a population-based study where exposure was not controlled (Hanrahan et al. 1984[131]) as the basis for their

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[125] 2022 Draft Assessment at 2-4, Table 2-1.
[126] NASEM 2011 at 52.
[127] 2022 Draft Assessment (Appendix) at D-19.
[128] Wolkoff P, Nielsen. 2010. Non-cancer effects of formaldehyde and relevance for setting an indoor air guideline. Environment International 36 (7): 788-799.
[129] Nielsen GD, Wolkoff P. 2010. Cancer effects of formaldehyde: a proposal for an indoor air guideline value. Archives of Toxicology, 84(6): 423-446.
[130] Lang I, Bruckner T, Triebig G. 2008. Formaldehyde and chemosensory irritation in humans: a controlled human exposure study. Regulatory Toxicology and Pharmacology, 50(1):23-36.
[131] Hanrahan LP, Dally KA, Anderson HA, Kanarek MS, Rankin J. 1984. Formaldehyde vapor in mobile homes: a cross sectional survey of concentrations and irritant effects. American Journal of Public Health, 74(9): 026-1027.

evaluation and cite Hanrahan et al. (1984) and several older studies (Kulle et al. 1993[132] or Andersen and Molhave 1983[133]) as offering support.

Importantly, as Drs. Kaden and Wolkoff point out, the higher quality studies either did not find any effect even at the highest exposure, or found only found mild, chemosensory effects. They express dismay that studies considered the "gold standard" for setting safe exposure limits were ignored because effects were not observed and asked that EPA rely on the higher quality studies rather than on older, lower-quality work.

In their comments on the 2022 Draft Assessment, Golden and Holm raise a number of these same concerns with EPA's approach to sensory irritation in the 2022 Draft Assessment:

- EPA's Reliance on Residential or Home studies is Misguided and is not the Best Available Science
- EPA Should Rely on Human Volunteer Chamber Studies that have Proper Controls to Reduce or Eliminate Confounding Factors and False positives
- EPA Fails to Rely on Mueller et al., 2013, and Lang et al., 2008, that are considered by many countries as "critical studies."
- EPA's representation of the Sensory Irritation Studies as an Adverse Health Effects cannot be considered the Best Available Science

Golden and Holm point out that EPA's reliance on studies conducted in residential settings rather than those conducted under controlled conditions was criticized by NASEM (2007) and runs contrary to recommendation of other authoritative bodies. They point out limitations in basing conclusions on studies in residential settings. They also point out the issues with using older chamber studies with poorer study design, particularly when odor detection may influence reporting unless the odor is somehow masked. Formaldehyde's characteristic acrid or pungent odor can be detected at concentrations below those that produce the symptoms of sensory irritation.

Golden and Holm recommend that an exposure limit of 0.3 ppm formaldehyde in indoor air is conservative, health protective, and supported by high quality studies.

C. EPA discounted studies considered key by other authoritative bodies in favor of older studies with less robust study designs.

From the authoritative assessments and reviews published prior to 2019 (ANSES 2018, 2019; Danish Ministry of the Environment 2014; ECHA 2016, 2019; SCOEL 2016; EPA 2008, 2010; WHO 2010), there is a consistent identification of the Lang et al. (2008) and Mueller et al. (2013) studies as key for defining the most sensitive endpoints from which to derive acceptable concentrations of formaldehyde following acute/short-term inhalation exposures. The

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[132] Kulle TJ. 1993. Acute odor and irritation response in healthy nonsmokers with formaldehyde exposure. Inhalation Toxicology, 5(3): 323-332.

[133] Andersen I, Molhave L. 1983. Controlled human studies with formaldehyde. In: Gibson JE (ed) Formaldehyde Toxicity. Hemisphere Publishing, Washington DC. ***Note, this study is a book chapter and thus not peer reviewed.***

authoritative bodies identified these two studies because they are high-quality studies, where exposure concentrations were known and controlled, exposures were randomized and double-blinded, and individuals served as their own controls. They noted the studies included both subjective and objective measures, and individuals who were identified as being hyper- or hypo-sensitive to the effects of formaldehyde. Importantly, there is no evidence indicating an increased sensitivity to sensory irritation to formaldehyde among people often regarded as susceptible (asthmatics, children, and older people) (WHO 2010).

Although some (for example, ECHA 2019) have criticized these two studies as having a small number of volunteers (10 males and 11 females for Lang et al. 2008; 45 males for Mueller et al. 2013), together they provide a large and consistent dataset for human response. The large variability noted by critics is a consequence of using a genetically diverse human population for a subjective endpoint. Furthermore, earlier controlled human exposure studies (Andersen and Mohave 1983, Kulle 1993, Krakowiak et al., 1998) and studies in occupational populations (Alexandersson and Hedenstierna 1988, Horvath et al, 1988) support the results.

> These OELs [occupational exposure limits] for formaldehyde are based on two key studies (Lang et al. 2008; Mueller et al. 2013). These values have been used by France in their RMOA [regulatory management option analysis]. Registrants of formaldehyde updated their CSR17 in December 2015, proposing the following DNELs [derived no effect level] to be considered for risk characterisation: 0.3 ppm for long-term exposure and 0.6 ppm for short-term exposure, based on the key studies. The long-term DNEL is supported by mathematical risk extrapolations from experimental animals to humans. Considerations related to the assessment of excess cancer risk are reported in section 2 above.
> — ECHA 2019

> The most relevant controlled studies of Lang et al. (2008) and Mueller et al. (2013) took into consideration objective signs of sensory irritation (eye blinking rate, nasal resistance and flow), influence of personality factors and confounding by odor (Lang study). According to the identification of objective signs of ocular and nasal sensory irritation, which are the most sensitive effects, the NOAEC [no observed adverse effect concentration] is set at 0.3 ppm and is chosen for the derivation of long-term DNEL. No AF [adjustment factor] is applied as epidemiological data show that formaldehyde vulnerable occupational subpopulation were already considered in the Lang and Mueller studies. Besides, sensory irritation is a precursor key event providing a margin of safety for the onset of more severe irritative effects of formaldehyde.
> — ANSES 2019

> The eye irritation being the most sensitive parameter Lang et al. (2008) performed a study using subjective questionnaire ratings and objective methods.... Human exposure studies indicate that 615 $\mu g/m^3$ is the threshold for trigeminal stimulation

of the eyes (e.g. increased blink frequency) and 369 $\mu g/m^3$ is the threshold for subjective sensory irritation (Lang et al, 2008; WHO, 2010).
— Danish Ministry 2014

In this respect, numerous studies, comprising in total more than 400 volunteers, have addressed human sensory irritation effects of FA [formaldehyde]. The Paustenbach et al (1997) review [and two similar reviews of Bender (2002) and Arts et al. (2006)], concluded that sensory irritation would seldom be observed at 0.5 ppm FA and extrapolated these results to suggest that a limit of 0.3 ppm would prevent sensory irritation in nearly all occupational exposed individuals. Two recent chamber studies (Lang et al. 2008; Mueller at al. 2013) found no pure sensory irritation, as measured by objective parameters, in the concentration range from 0.5 to 0.7 ppm at a constant exposure to FA during a 4-hour period. Both studies applied slightly different concentration regimes. Exposures with 4 superimposed peaks being most relevant for derivation of an OEL with STEL were 0.3 ppm + peaks of 0.6 ppm and 0.5 ppm + peaks of 1 ppm in the Lang study, and in that of Mueller 0.3 ppm + peaks of 0.6 ppm and 0.4 ppm + peaks of 0.8 ppm. Objective signs of irritation were only observed at 0.5 ppm + peaks of 1 ppm. Because 0.3 ppm + peaks of 0.6 ppm was a consistent NOAEC in both of these investigations this exposure regime is taken forward for derivation of the OEL, TWA [time-weighted average] with STEL[short-term exposure limit]. The recent study (Mueller et al. 2013) was conducted with hypo- and hyper-sensitive individuals, who showed no difference in sensory irritation sensitivity to FA, but the hypersensitive individuals reported significantly higher effects for olfactory induced symptoms as 'perception of impure air.'
— SCOEL 2016

D. Sensory Irritation and Other Annoyance Endpoints are Inappropriate endpoints for developing RfCs

Sensory irritation of the eyes and upper airways are not considered *adverse* by authoritative bodies and reviews (WHO, 2010; Nielsen et al., 2017; ECHA, 2019a). Perception of, or sensory stimulation by, an irritating substance would not be considered adverse as perceptions of, or stimulations by, an unpleasant smell do not affect the form or function of the tissue or organism.

Eye and nasal tract chemosensory detection and nerve stimulation that results from inhalation exposure to formaldehyde is an example of chemesthesis. Chemesthesis is a normal physiological response without functional impairment or pathological change. Thus, sensory recognition of formaldehyde is not adverse and is similar to sensory responses to other chemicals or environmental stimuli such as tearing when exposed to fumes from cut onions or blinking when suddenly exposed to sunlight.

As EPA acknowledged in the 2022 Draft Assessment, formaldehyde irritation effects may be mediated by neuronal receptors such as TRPA (a family of transient receptor potential ion channels). Like other irritants such as mustard oil, cinnamaldehyde, and metabolites of environmental pollutants such as styrene, ozone, naphthalene, and acrolein, formaldehyde

activates the TRPA1 ion channel by covalent interactions resulting in pain (reviewed by NASEM 2011). Like odor detection, such chemesthesis reactions represent a sensory process and should not be considered histopathologically detectable irritation (i.e., an inflammatory response) or an adverse health effect (reviewed in NASEM 2011). The WHO (2010) notes that the TRPA1-mediated response occurs quickly, so longer exposures (i.e., beyond the 4 hours in the chamber studies of Lang et al., 2008 and Mueller et al 2013) are not anticipated to increase the response.

In addition to these studies of irritation following short-term exposures, multiple studies have also been conducted in animals focused on objective measurements of tissue irritation, cell proliferation and cytotoxicity following short-term repeated dose exposures (Swenberg et al. 1983a, 1983b; Monticello et al. 1991; Monteiro-Riviere and Popp 1986). Although some of these studies were discussed by EPA under the category "respiratory pathology" with robust evidence, they are objective evidence of an adverse effect, tissue irritation, following short-term exposures and would thus be more relevant for deriving an irritant RfC.

In their comments on the 2022 Draft Assessment, Golden and Holm noted that EPA has chosen to rely on studies published in the 1980s (Hanrahan et al, 1984, Kulle et al., 1987) to identify a POD, instead of relying on state-of-the-art studies that were published this century (Mueller et al., 2013, Lang et al., 2008). According to EPA, in the more recent studies, it was '[d]ifficult to define an adverse response level cutoff for these endpoints," which aligns with the difficulty in categorizing these low concentration sensory effects as adverse.

As described above, however, other reviews that included Mueller et al. and Lang et al. did not have these perceived difficulties. For example, the European Commission Scientific Committee on Occupational Exposure Limits (SCOEL) noted that with the availability of two volunteer exposure studies complementing each other and not only measuring subjective reporting but also objective signs of eye and upper respiratory tract irritation (Lang et al., 2008; Mueller et al., 2013), an "exposure limit" can now be based on objective parameters not potentially biased by personality traits like anxiety or expectations.

E. EPA should use objective measures of adverse effects for developing noncancer RfCs

Studies in which sensory irritation was evaluated in humans also provided some objective measurements of tissue irritation or lung function. To date, multiple studies that collectively included more than 400 people have addressed sensory irritation in humans following acute exposures to inhaled formaldehyde. Two controlled human exposure studies (Lang et al. 2008; Mueller et al. 2013) provide the most compelling evidence for the impacts of acute/short-term exposures.

Both studies exposed human volunteers to formaldehyde for 4-hour periods with some superimposed peak periods of 15-minute exposures to higher concentrations to simulate occupational exposures. In both studies, each individual was exposed in a randomized, double-blinded manner, on different days, to all exposure conditions. The exposures in the Lang et al. (2008) study were 0, 150, 300, or 500 ppb formaldehyde, with multiple transient exposures of short-term duration ranging from 600 to 1,000 ppb. The exposures in the Mueller et al. (2013) study were 10 ppb (background air), 500 ppb, or 700 ppb formaldehyde as a constant exposure,

or 300 ppb or 400 ppb formaldehyde as a constant exposure with multiple transient exposures of 600 ppb or 800 ppb. The Mueller et al. (2013) study also included individuals who were considered hypersensitive to formaldehyde irritation. Various objective measures (conjunctival redness, blinking frequency, nasal flow and resistance, pulmonary function, and reaction times) were assessed.

- In the Lang et al. (2008) study, the only significant objective impacts from formaldehyde exposure were irritation symptoms -- slight-to-moderate blinking frequency and conjunctival redness were reported when there were transient exposures of 1,000 ppb superimposed on top of baseline exposure of 500 ppb formaldehyde. Objective symptoms reversed within 16 hours after the end of the exposures.
- In the Mueller et al. (2013) study, none of the subjective rating of symptoms and complaints were seen at any of the exposure scenarios (even up to 800 ppb) in either hyper- or hyposensitive individuals.

From these studies, a No Observable Effect Level (NOEL)[134] of 700 ppb for 4 hours, as well as 400 ppb for 4 hours with 15-minute peaks of 800 ppb, was established. A NOEL was established, rather than a NOAEL, since these endpoints were not considered adverse effects. This NOEL is valid for individuals who are identified as hyper- and hypo-sensitive. Combined, these studies indicate a NOAEL (emphasis added) of 700 ppb (4-hour exposure), based on lack of pulmonary function changes at even this highest exposure concentration.

Nevertheless, EPA chose to derive RfC measurements for sensory irritation from the objective measure of "burning eyes" in a group of teenagers and adults in residential settings (Hanrahan et al., 1984) and self-reported irritation symptoms in controlled human exposure studies (Andersen and Molhave, 1983 [n=16]; Kulle et al., 1987 [n=10]) where the distinctive odor of formaldehyde was not masked were used to develop (benchmark concentration) BMC/2s (Andersen and Molhave, 1983; Kulle et al., 1987) and BML_{10} (Hanrahan et al., 1984), with additional 10-fold uncertainty factors applied. This led to a RfC for sensory irritation of 0.009 mg/m^3 based on the Hanrahan et al. (1984) study.

Asthma

A. EPA's weight of evidence conclusions regarding inhalation of formaldehyde and asthma are not scientifically justified and not based on the best available science.

In the 2022 Draft Assessment, EPA integrated evidence for the prevalence of current asthma for children and adults and concluded that the evidence was moderate for asthma based on elevated risks in eight medium confidence studies of current asthma in adults and children. The EPA concluded that "inconsistencies in study results appear to be explained by exposure levels" as evidenced by:

[134] Note, this is a No Observable Effects Level, rather than a No Observable Adverse Effect Level (NOAEL)

- No elevated risk of current asthma in six high and medium confidence studies with relative low exposures (<0.05 mg/m^3) but associations with adequacy of asthma control were observed in one study at this lower exposure levels.
- Strongly elevated risks in three medium confidence studies in occupational settings with exposures form 0.1 to >0.5 mg/m^3.

EPA's integration of evidence is overly simplistic. Asthma is widely recognized as a heterogeneous group of diseases based on clinical features, physiological characteristics, and varying outcomes ranging from mild to severe. Variation in response to different asthma treatments also suggests that there are multiple mechanisms and pathways that are relevant to the development and exacerbation of asthma. It is not a single disease entity. EPA does not adequately address potential differences in asthma phenotypes that likely represent different underlying biological mechanisms for asthma development.

EPA does not describe how the postulated mechanistic pathways are potentially related to different asthma phenotypes. There is a large body of ongoing research focused on improving the understanding of the specific biological mechanisms (or endotypes) that are associated with phenotypes (for example, see Akar-Gibril et al. 2020; Berdine et al. 2020; Carr et al. 2018; Kuruvilla et al. 2019; Kaur and Chupp 2019; Conrad et al. 2021; Schoettler and Strek, 2020; McDowell and Heaney 2020; Lötvall et al. 2011; Wenzel et al. 2012).

As a result of differences in phenotypes and endotypes, there are likely different mechanisms (and different modes of action) by which formaldehyde could potentially increase risk. At the very least, the evidence related to potential mode of action should be synthesized separately for occupational asthma (a phenotype that is generally not related to atopic or allergic asthma). Differences in potential mechanisms and the pathogenesis for early onset/atopic asthma versus early onset/non-atopic asthma could also be described (even if these groups cannot be distinguished in the existing epidemiologic studies). Collectively, these differences, which are not related to differences in exposure concentrations, potentially explain inconsistencies in results.

Two studies were selected to derive a point of departure (POD) for current asthma (Annesi-Maesano et al. 2012; Krzyzanowski et al. 1990); however, neither study showed clear associations between current asthma and formaldehyde exposure.

- Annesi-Maesano et al. (2012) was selected to derive a POD for current asthma; however, there is no association reported between formaldehyde exposure and atopic asthma or non-atopic asthma (see Annesi-Maesano et al. 2012, Figures 5 and 6).
- Krzyzanowski et al. (1990) reported an association between formaldehyde exposure and current asthma; however, after stratifying by exposure to secondhand smoke, there was no association between formaldehyde exposure and current asthma among children who were not exposed to tobacco smoke; the association between formaldehyde exposure and asthma was only observed among children exposed to tobacco smoke.

Two studies were selected to derive a POD for poorly controlled asthma (Dannemiller et al. 2013) and Venn et al. (2003). These studies only reported correlations between formaldehyde concentrations and poorly controlled asthma. Both studies were cross-sectional studies that relied

on response to questionnaires for the identification of poorly controlled asthma. Neither study controlled for potential confounding by indoor allergens that trigger asthma.

- Dannemiller et al. (2013) was based on short-duration sampling measured after the time that the severity of asthma was measured. The short-duration sample was assumed to represent long-term exposure.
- Venn et al. (2003) measured persistent wheezing illness in case-control study of 9-11 years old children. There was no effect of formaldehyde on risk of persistent wheezing illness, before or after adjusting for age, sex, and Carstairs deprivation index. However, the odds ratios for persistent wheezing illness increased with increasing exposure to a damp living room (identified as very low, low, moderate, and high), and the trend was also statistically significant.

There are numerous environmental exposures that are triggers for asthma including secondhand smoke, dust mites, molds, cockroaches and pests, pets, nitrogen dioxide, outdoor air pollution, and wood smoke.[135] The overwhelming majority of epidemiologic studies were cross-sectional designs that did not consider or adjust for these potential asthma triggers in indoor air.

The 2022 Draft Assessment also appears to contain errors in the text:

- The 2022 Draft Assessment states that the EPA conducted a meta-analysis to calculate a summary effect estimate for similar results[136]; there is no further information, and no summary effect estimates are reported.
- Figure 1-11, Panel C: Effect Modification of Prevalence of Current Asthma in Children by Atopy Status) shows increased risks (odds ratios > 3.0) for both atopic and non-atopic asthma in the highest exposed group (>0.06 mg/m^3, which also appears to be mislabeled as $\mu g/m^3$). These odds ratios do not match the results presented in Annesi-Maesano et al (2012). Annessi-Maesano et al. (2012) reported odds ratios of 0.96 and 0.82 for the prevalence of current asthma in the highest exposed group for atopic children and non-atopic children, respectively.

1. EPA's Conclusions on Asthma are Contrary to NASEM (2000) and Kanchongkittiphon et al. (2015)

Not only did EPA ignore the two relevant publications by Drs. Golden and Holm, the 2022 Draft Assessment also ignored evidence on the key substances that are considered causally related to asthma. In doing so, the 2022 Draft Assessment presents conclusions that are at complete odds with NASEM (2000) (an authoritative review for the endpoint of asthma) and Kanchongkittiphon et al. (2015) (a comprehensive update involving 69 additional studies focused on indoor environmental exposures and exacerbation of asthma), both of which demonstrated a practical weight of evidence approach.

Most of the research on asthma addresses "asthma exacerbation," or the onset or worsening of symptoms—some combination of shortness of breath, cough, wheezing, and chest tightness—in someone who already has developed asthma. In assessing potential exposures that might

[135] 2022 Draft Assessment.
[136] 2022 Draft Assessment at 1-81.

exacerbate asthma in children, NASEM (2007) identified potential causal relationships between asthma and the allergens produced by cats, cockroaches, house-dust mites, environmental tobacco smoke (ETS) exposure, dog allergen exposure, fungal exposure, and damp conditions or indicators of dampness (e.g., dust mite and fungal allergens).

It is well documented (i.e., Garrett et al., 1998, 1999; Rumchev et al., 2002, 2004) that other substances in indoor air (e.g., VOCs and fungal spores) can cause and/ or exacerbate respiratory symptoms quite apart from formaldehyde. For instance, acrolein, an aldehyde that is 200 times more potent as a sensory irritant than FA (Fowles and Dybing 2003) and ubiquitous in indoor air, was significantly associated with asthma, whereas FA was not (Annesi-Maesano et al. 2012). The implications of acrolein as a previously unrecognized confounder are that indoor air studies, which report associations between FA and childhood asthma, should be interpreted with caution unless/until potential contributions and/or associations with acrolein are also considered.

In addition, as noted by Leikauf (2002) due to ever-increasing acrolein emissions into the environment, acrolein as a direct irritant may increasingly become a health hazard in individuals with respiratory diseases such as asthma. A recent paper (Golden and Holm 2017) that was not cited or integrated into the Review supplies a roadmap of why unrecognized exposure to acrolein is an important confounding factor in many indoor air-related studies focused on formaldehyde.

Major sources of acrolein in indoor air include cooking with various oils at temperatures of 180°C (which generates 5-250 mg of acrolein/kg oil) and environmental tobacco smoke (ETS). In Hong Kong, acrolein emissions from commercial kitchens (at 7.7 tons/year) far exceeded the annual vehicle emissions of acrolein (1.8 tons/year) (Ho et al. 2006). In California, cooking events resulted in acrolein air concentrations ranging from 26.4 to 64.5 $\mu g/m^3$. Meanwhile, median creatinine urine levels for smokers were found to be 203 µg/g (compared to 78.8 µg/g for nonsmokers), thus reflecting substantial differences between smokers and nonsmokers with respect to acrolein exposure.

Therefore, there is inadequate or insufficient evidence to determine an association between indoor residential VOC exposures and the development or the exacerbation of asthma. These results highlight the need to investigate and focus on factors known to be causally associated with asthma exacerbations, rather than FA for which the evidence does not rise to this level of confidence. However, rather than conducting a full Weight of the Evidence evaluation on asthma and allergies, EPA reviews only a subset of the relevant literature to conclude that the "evidence indicates" that formaldehyde plays a role in "allergic conditions and current asthma symptoms or degree of asthma control." In doing so, EPA overlooks the significant influence of confounding factors in low FA air concentration studies.

The discovery that acrolein is virtually certain to have been present in the indoor air of all studies in which FA has been implicated as associated with asthma raises a red flag with respect to EPA's conclusions. Other than a single study Annesi-Maesano et al. 2012), none of the other studies currently relied upon with respect to the FA/asthma issue in childhood considered co-exposures to acrolein. Consequently, conclusions with respect to FA alone can only be considered as suspect. This is particularly the case since acrolein is a demonstrably more potent

respiratory tract irritant than FA, with the clear ability to exacerbate asthma symptoms. EPA must therefore revise the 2022 Draft Assessment to include a practical Weight of the Evidence evaluation on asthma using the best available science and must account for the contributing role of acrolein.

Finally, EPA's misrepresentation of the two studies (Krzyzanowski et al., 1990; Annesi-Maesano et al., 2012) it relied on to derive a POD cannot be ignored. EPA's bias against the chemical to even use a negative study in support of an association does not represent the best available science.

VI. Noncancer Health Endpoints: Systemic Effects

A. The Best Available Science Does Not Support EPA's Conclusions Regarding Formaldehyde and Reproductive and Developmental Effects

The NASEM (2011) Committee stated that EPA did not provide a clear weight of evidence discussion to support its classification for reproductive and developmental toxicity and did not agree with EPA's conclusions:

> The draft IRIS assessment states that epidemiologic studies provide evidence of a "convincing relationship between occupational exposure to formaldehyde and adverse reproductive outcomes in women." **The committee disagrees and concludes that a small number of studies indicate a suggestive pattern of association rather than a "convincing relationship."** … Animal data also suggest an effect, but EPA should weigh the negative and positive results rigorously inasmuch as negative results outnumbered positive ones for some end points, should evaluate study quality critically because some studies of questionable quality were used to support conclusions, and should consider carefully potential confounders, such as maternal toxicity, effects of stress, exposure concentrations above the odor threshold, and potential for oral exposures through licking.[137]

As discussed further below, EPA maintains a similarly strong conclusion regarding the reproductive and developmental evidence, despite the absence of new supportive sentinel studies published in the last decade or any plausible MOA.

Regarding the epidemiological evidence of female reproductive toxicity and birth outcomes, the 2022 Draft concluded, "Together, the findings among women provide moderate evidence of developmental *or female reproductive toxicity*."[138]

A close review of the epidemiological literature assessing formaldehyde exposure and developmental and reproductive outcomes is limited and subject to methodological limitations that substantially inhibit causal inferences. In the only two medium confidence studies (the

[137] NASEM 2011 at 10 (emphasis added)
[138] 2022 Draft Assessment at 1-382 (emphasis added)

remainder were low quality) assessing the risk of spontaneous abortions among women in occupations with potential formaldehyde exposure, self-reported questionnaires were used to ascertain both exposure (i.e., use of formaldehyde-based disinfectants in first trimester of pregnancy) and outcome (John et al. 1994, Taskinen et al. 1999).

Given the crude exposure surrogates used in these studies, lack of robust adjustment for potential confounders and covariates, and generally weak risk estimates, evidence of increased risk of reproductive effects is unconvincing. Further, epidemiological associations observed among formaldehyde exposed mothers and birth outcomes were inconsistent and primarily include low confidence studies. Two birth cohort studies were assigned medium confidence; one of the studies found no association with gestational age or birth (Franklin et al. 2019) and a second study demonstrated a stronger effect between total VOC exposure and birth weight and postnatal weight relative to formaldehyde exposure (Chang et al. 2017).

Regarding male reproductive toxicity, the 2022 Draft Assessment concludes that there is *slight* evidence that formaldehyde exposure is associated with lower total and progressive sperm motility, and delayed fertility and spontaneous abortion, but that the epidemiological literature was bolstered by *robust* evidence from experimental studies in animals.

Two medium confidence studies analyzed paternal formaldehyde exposure in relation to sperm quality parameters and risk of spontaneous abortion among men of Chinese Han ethnicity in the woodworking industry (Wang et al. 2012, Wang et al. 2015). While some evidence of increased odds of impaired progressive sperm motility and total motility were observed, statistically significant associations were generally not observed. Importantly, the temporal relationship between formaldehyde exposure and various reproductive outcomes could not be established.

Regardless of the inconsistent results, the findings may lack generalizability outside of the specific population that was surveyed (i.e., Chinese Han men employed in the woodworking industry). Similarly, while EPA indicates that animal evidence is robust, there were limitations in these studies that impact their utility, including failure to adhere to agency guidance for reproductive toxicity studies. Further, the critical studies indicated findings of unclear clinical relevance – i.e., Ozen et al. (2002) reported no reductions in relative testes weight that exceeded 10% (often used as a generic cutoff for biologically meaningful weight changes); the decreases appear in the 2-3% range.

The 2022 Draft Assessment provides a lengthy discussion of potential MOAs for reproductive and developmental toxicity. Because formaldehyde is not systemically distributed, it cannot reach reproductive tissues or the developing organism. The postulated MOAs include indirect oxidative stress "possibly linked to inflammatory responses," or neuroendocrine-mediated mechanisms, such as disruption of the hypothalamic-pituitary-gonadal (HPG) axis. These postulated MOAs are based on a few studies of mixed confidence (including several low confidence studies). The 2022 Draft Assessment acknowledges the lack of data, noting "a stressed induced mechanism might contribute to adverse outcomes on the reproductive system

and development in the absence of systemic distribution of formaldehyde"[139] and that there is "no definitive data identified that define an MOA." [140]

Nonetheless, the 2022 Draft Assessment concludes that:

> Overall, the **evidence indicates** that inhalation of formaldehyde likely causes increased risk of developmental or female reproductive toxicity in humans, given the appropriate exposure circumstances." And "Likewise, the **evidence indicates** that inhalation of formaldehyde likely causes increased risk of reproductive toxicity in men, given the appropriate exposure circumstances…"[141]

Considering that EPA judged the animal evidence as "indeterminate," the epidemiological evidence was "moderate," (and arguably, should also be considered indeterminate), and there is no established plausible MOA, the weight of evidence does not support EPA's evidence integration judgements for reproductive or developmental toxicity.

During the truncated interagency consultation on the 2022 Draft Assessment, other federal agencies disagreed with EPA's conclusions on systemic effects from formaldehyde exposure (e.g., myeloid leukemia, reproductive effects). ATSDR noted that without supportive mechanistic evidence for female reproductive toxicity, overall evidence finding should be downgraded to evidence suggests.

B. The Best Available Science is not "suggestive evidence" of Nervous System Effects from Formaldehyde

The 2022 Draft Assessment stated, "Overall, conclusive of a nervous system health hazard in humans exposed to formaldehyde was not identified (i.e., **suggestive evidence**).[142] The finding of "suggestive evidence," however is at odds with EPA's acknowledgement of inconclusive evidence. Indeed, a critical review of the available evidence suggests that an "inadequate" descriptor would be more appropriate for this endpoint.

For example, regarding developmental neurotoxicity, there are only two studies that EPA judged as medium confidence. However, these two publications are actually a single study, because both publications are based on the same data set (Sarsilmaz et al. 2007; Aslan et al., 2006). More importantly, the data were analyzed on a pup basis rather than litter basis, and there were only three litters. Thus, the authors were unable to control for litter effects; using the litter rather than the pup as the statistical unit is incompatible with EPA and OECD 426 neurodevelopmental

[139] 2022 Draft Assessment at 1-428
[140] 2022 Draft Assessment at 1-429
[141] 2022 Draft Assessment at 1-383
[142] 2022 Draft Assessment (Overview) at 76

testing guidelines (EPA Guidelines for Neurotoxicity Risk Assessment, 1998[143]; OECD 426[144]). Additionally, the study exposed pups after birth to attempt to correspond to the third trimester of human neural development.

In Sarsilmaz et al. (2007) there was substantial variability in the measure of pyramidal cell layer in the control group, which could have affected results given the small sample size. When the endpoint was normalized to postnatal day 90 (PND90), there was no significant difference between controls and formaldehyde-exposed animals.

In sum, there is only one "study" for the developmental neurotoxicity endpoint, which was not conducted according to guidelines, was not actually *in utero* exposure, and suffered from other limitations.

Epidemiological studies are also limited, including seven studies of amytophic lateral sclerosis (ALS) with no exposure characterization (a key deficiency), with few statistically significant associations reported (n = 2) and multiple null studies. Other generally poor-quality studies of neurobehavioral tests of memory, dexterity, and psychomotor function provide little insight into potential formaldehyde neurotoxicity.

As with reproductive and development effects, discuss previously, EPA has not identified any data supported MOA for any nervous system effect. The 2022 Draft Assessment relies instead on four "hypothesized" MOAs for these effects, including activation of sensory nerves; neuronal activation in the olfactory epithelium; altered hypothalamus-pituitary-adrenal gland (HPA) axis signaling; and changes in neuronal health and function due to indirect CNS oxidative stress or excitatory changes, which would necessitate a cascade of cellular responses in the nose that could reach the brain.

Further, there are many normal processes and exposures that can cause oxidative stress, and the body has compensatory mechanisms to account for such changes. After much speculation on this MOA, the 2022 Draft Assessment underscores the lack of data: "In general, an explanation for oxidative stress-related changes in the absence of systemic distribution of formaldehyde or very high formaldehyde exposure levels is unavailable, limiting the feasibility of this potential mechanism."[145]

Given the lack of data for any postulated MOA and failure to demonstrate consistent effects across any endpoint, an integration judgment of "evidence is inadequate" is more appropriate rather than the proposed "suggestive" integration judgment for nervous system effects.

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[143] North American Free Trade Agreement (NAFTA) Technical Working Group on Pesticides (TWG). 2016. Developmental Neurotoxicity Study Guidance Document. https://www.epa.gov/sites/default/files/2017-02/documents/developmental_neurotoxicity_study_internal_guidance_document_final_0.pdf

[144] OECD (2007), *Test No. 426: Developmental Neurotoxicity Study*, OECD Guidelines for the Testing of Chemicals, Section 4, OECD Publishing, Paris, https://doi.org/10.1787/9789264067394-en.

[145] 2022 Draft Assessment at 1-377.

VI. EPA failed to adhere to EPA policy, procedural and legal requirements in developing the 2022 Draft Assessment: Part 2

It is important to begin by recognizing that/ the IRIS Program is in need of improvement and that the Program has been undergoing reform under the auspices of the National Academies for a number of years. The Integrated Risk Information System (IRIS) program was never authorized by Congress. It was created by EPA with the goal of fostering consistency in the evaluation of chemical toxicity across EPA, providing potential regulatory inputs in the form of hazard identification and dose-response assessments. These two elements are intended to be taken and used by programs both within and outside of EPA for risk management activities undertaken for regulatory processes. This background adds even more significance to procedural, science policy, and methodological concerns raised by peer reviewers or attempted to be resolved in the abstract by sub-regulatory Agency documents and guidance.

Indeed, an impetus for IRIS reform was the 2011 critical review of the 2010 Draft Assessment of formaldehyde by an ad hoc Committee of the National Academies of Science, Engineering and Medicine (NASEM).[146] Importantly, the report issued by NASEM included a roadmap for revising the IRIS assessment process. Further process-oriented reviews of the IRIS program and a draft handbook in 2014,[1] 2018,[147] and 2022[148] also identified important areas for improvement with respect to several critical areas, including problem formulation, evaluation of study quality, and evidence integration.

When developing regulations, an agency needs to consider the best available method for achieving its regulatory objective. In determining the best method, an agency needs to utilize the best available information, including scientific, technical, economic or some other type. An agency needs to ensure that the record is complete, that all available information has been gathered from relevant sources, and that important perspectives and viewpoints are appropriately considered. An agency needs to examine the relevant data and articulate a satisfactory explanation for taking a specific regulatory action, including a rational connection between the facts found and the choice made. Furthermore, an agency would also need to provide a reasoned explanation for why its choice of policy appears to disregard facts and circumstances that were raised or identified in the information gathering process. If this careful, deliberative, transparent and deliberative process is not followed, a regulation may suffer from fatal legal flaws.

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[146] National Research Council. 2014. Review of EPA's Integrated Risk Information System (IRIS) Process. Washington, DC: The National Academies Press. https://doi.org/10.17226/18764.

[147] National Academies of Sciences, Engineering, and Medicine. 2018. Progress Toward Transforming the Integrated Risk Information System (IRIS) Program: A 2018 Evaluation. Washington, DC: The National Academies Press. https://doi.org/10.17226/25086

[148] National Academies of Sciences, Engineering, and Medicine 2022. Review of U.S. EPA's ORD Staff Handbook for Developing IRIS Assessments: 2020 Version. Washington, DC: The National Academies Press. https://doi.org/10.17226/26289

Given the longstanding problems with the IRIS Program, and given that these problems were highlighted by the 2010 Draft Assessment of formaldehyde, a new 2022 Draft Assessment should reflect the highest scientific quality. EPA would also adhere to the requisite steps to ensure the integrity of the process. As described in these comments, however, EPA has deviated from policies and standard practices and methodologies. No reasoned explanation has been provided as to why deviation from accepted practice or failure to address issues and incorporate available information occurred. Given that IRIS assessments often form the scientific foundation for regulatory actions, any regulatory action taken using the 2022 Draft Assessment, if finalized without change, will itself be flawed - procedurally, scientifically, and legally.

The integrity of the process, which influences the quality and scientific defensibility of the final work product is not an academic exercise. For example, IRIS values, even when still draft, are sometimes used by state and local agencies in regulatory actions.[149] Moreover, EPA programs, such as the hazardous air pollutant program under section 112 of the Clean Air Act, prioritize IRIS values for use in regulatory settings. As detailed in ACC's Reconsideration comments on the Miscellaneous Organics NESHAP, at the rulemaking stage, EPA may treat issues as resolved in the IRIS development process regardless of what flaws commenters on the rule may illuminate.[150]

For these reasons, it is important that the Agency, in developing its draft assessments and presenting them for peer review, follow all of its procedural requirements and ensure that interested parties are provided adequate opportunity to participate. For the reasons described below, EPA should reset its review process and conduct it in a manner that addresses the concerns raised herein.

A. EPA impermissibly deviated from key steps in its established IRIS process

EPA's IRIS process for developing human health assessments consists of seven steps: 1) Scoping and Problem Formulation/Draft Development; 2) Agency Review; 3) Interagency Science Consultation; 4) Public Comment/External Peer Review; 5) Revision of Assessment; 6) Final Agency Review and Interagency Science Discussion and 7) Finalization of the Assessment.[151] These established steps are intended to provide a degree of predictability and transparency to the assessment process. They allow for ample input from all stakeholders, whether in the public sector, within the EPA, or from other interested agencies. When the Agency does not follow its process, it needs to explain why it is deviating, which it has not done

[149] https://www.americanchemistry.com/industry-groups/formaldehyde/resources/acc-epa-misuse-of-draft-iris-assessment-letter.
[150] https://www.regulations.gov/comment/EPA-HQ-OAR-2018-0746-0320.
[151] https://www.epa.gov/iris/basic-information-about-integrated-risk-information-system#process

here. In the context of the 2022 Draft Assessment, EPA failed to follow this protocol from the outset.

The first step in the IRIS assessment process is Scoping and Problem Formulation/ Draft Development. EPA's own IRIS process outlines a series of steps that EPA must follow in developing a draft assessment:

1. Before beginning to develop a draft assessment, EPA undertakes scoping to identify the specific needs for an assessment.
2. Scoping is followed by the formulation of the scientific questions that will be the focus of systematic reviews conducted as part of assessment development.
3. EPA then releases these scoping and problem formulation materials as an "assessment plan."
4. A public meeting is held and there is an opportunity to comment so that the scientific community and the general public can provide input.
5. EPA then begins work to develop a draft by conducting a comprehensive search and systematic review of the scientific literature. During early stages of draft development, EPA provides the protocol which presents methods for conducting the systematic review and dose-response analysis to the public and an opportunity for public input on these materials.

In developing the 2022 Draft Assessment, EPA failed to fully implement this first step. EPA never released an IRIS assessment plan, which would have included scoping and problem formulation materials. Rather, on its website it states that this step is "not applicable" without explaining why this step is not applicable. By not following the IRIS process, EPA denied the public multiple opportunities to provide valuable input into key formative elements of the 2022 Draft Assessment. Consequently, the 2022 Draft Assessment was not based on a fully developed record of available information.

For example, had EPA followed this process it would have incorporated, or explained why it was not incorporating a number of important studies, reviews, and responses, including several dozen that ACC has submitted to EPA for its consideration since 2010. Appendix A identifies 68 key studies, reviews, or responses that EPA excluded from the main text or supplemental information of the 2022 Draft Assessment. This includes nearly 60 key publications missing entirely from the main text. Most of these items have been presented to EPA by the ACC Formaldehyde Panel in correspondence and presentations since 2010. A basic literature search should have identified these studies, and EPA should have explained how it was addressing these references. In addition, several key studies and reviews, with several examples in appendix A, are cited by EPA in the main text or appendices but then cursorily dismissed with a footnote, parenthetical, or a single sentence.

1. **EPA has not provided any reasoned explanation for treating this situation differently than other reviews.**

EPA has inconsistently applied its IRIS process as well as related policies and peer review recommendations in developing and reviewing recent draft IRIS assessments:

- Based on a review of EPA's "IRIS Program Outlook," which describes assessments that are currently in development, formaldehyde is the only one of the sixteen chemicals under review by the IRIS Program for which EPA has not released an IRIS Assessment Plan or Systematic Review Protocol for public comment prior to the release of a draft assessment.[152] This deviation is cause for concern that the foundational elements for the review were developed without soliciting or incorporating valuable information from stakeholders.
- EPA has inconsistently applied its IRIS problem formulation process under Step 1, including failing to release an IRIS assessment plan or systematic review protocol as well as failing to hold a public meeting and take public comment on these documents. According to EPA's February 2022 IRIS Outlook, the other 15 chemicals being reviewed by the IRIS Program all will have chemical-specific systematic review protocols prior to the draft assessment and over half of the chemicals have a scheduled IRIS assessment plan (with public comment opportunities for both).[153] These steps are laid out in EPA's IRIS process website,[154] EPA's draft IRIS Handbook,[155] and NASEM review of the Handbook.[156]
- As the ACC Formaldehyde Panel's recently denied request to extend the comment period demonstrated,[157] EPA's approach to public comment here is notably different from other recent draft assessments, including assessments for vanadium, perfluorobutanoic acid, and ammonium perfluorobutanoic acid, in which comment period extensions were granted. Similarly, the 2010 Draft Assessment for formaldehyde included a 90-day public comment period along with a public listening session. Additionally, under the review process for other IRIS assessments, EPA has provided multiple opportunities for public comment, 90 days for comment on draft assessments, and a public listening session. For the 2022 Draft Assessment, however, EPA has only provided 60 days for public comment on a two-thousand-page assessment, despite requests from stakeholders and

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[152] https://www.epa.gov/iris/iris-program-outlook

[153] https://www.epa.gov/system/files/documents/2022-02/iris-program-outlook_feb-2022.pdf.

[154] "Draft development begins with a comprehensive search and systematic review of the scientific literature. During early stages of draft development, EPA provides the assessment protocol which presents methods for conducting the systematic review and dose-response analysis to the public and an opportunity for public input on these materials.... EPA releases these scoping and problem formulation materials (i.e., IRIS assessment plans) and then a public meeting is held to obtain input from the scientific community and the general public." https://www.epa.gov/iris/basic-information-about-integrated-risk-information-system#process.

[155] "The draft Assessment Plan is presented at a Public Science Meeting to solicit scientific and stakeholder input. The Public Science Meeting may be held in person or virtually. Any revisions to the specific aims and PECO resulting from the public comments will be reflected..." https://ordspub.epa.gov/ords/eims/eimscomm.getfile?p_download_id=541571.

[156] "In a systematic review, the protocol is a complete account of planned methods, which should be registered prior to conduct of the review." https://nap.nationalacademies.org/download/26289.

[157] https://www.americanchemistry.com/industry-groups/formaldehyde/resources/extension-request-on-draft-iris-toxicological-review-of-formaldehyde.

members of Congress for additional time. This truncated public comment period, therefore, denied the public the opportunity to adequately comment on the 2022 Draft Assessment.

- In the recent peer review of EPA's draft IRIS assessment for perfluorohexanoic acid, EPA and its reviewers relegated epidemiology to a lesser role, and rightly focused on the need to look at the modes of action, which is in stark contrast to EPA's treatment of epidemiological data for cancer and noncancer endpoints in the 2022 Draft Assessment and on MOA.[158]

1. Interagency science consultation process for EPA's 2022 Draft Assessment undermines transparency and did not elicit information from potentially impacted agencies

At Step 3 of its process, EPA solicits input from other federal agencies. In this case, EPA provided other federal agencies only four weeks to respond to its voluminous materials. While this time would be short under normal circumstances, EPA's 30 days included the period from Christmas through New Year's, a period when many in the federal government are out of the office, further reducing the actual time available for other agencies to review. Perhaps as a result of this, several federal agencies from whom responses should have been expected, did not respond. Given the lack of a clear record on the review, however, we are unable to discern why these agencies did not respond. For this reason, and others discussed below, EPA should reengage with other federal agencies to ensure it has obtained their considered opinions.

Interagency consultation is extremely important. Federal agencies are the repositories of significant substantive expertise and experience. Interagency coordination ensures that actions taken by one agency do not conflict with the policies or actions of another agency, which could lead to inconsistent, incompatible, or duplicative policies. The interagency review process provides for identification and then aggregation of views and perspectives from numerous federal agencies. Additionally, it allows an agency to receive the specialized knowledge held by other agencies with related or overlapping jurisdiction.

Truncated coordination also runs contrary to several recommendations of the Administrative Conference of the U.S. (ACUS,) of which both EPA and OIRA are members.[159]ACUS is "an independent federal agency within the executive branch charged with convening expert representatives from the public and private sectors to recommend improvements to administrative process and procedure."[160] In its recommendations on Improving Coordination of Related Agency Responsibilities,[161] ACUS notes that "[p]romoting consistency is already explicitly within the mandate" of OIRA under Executive Order (E.O.) 12866 and subsequent Orders.

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[158] https://insideepa.com/tsca-news/panel-lauds-iris-pfas-assessment-doubts-chemical-specific-approach?s=na.
[159] https://www.acus.gov/directory/public-member.
[160] https://www.acus.gov/about-acus.
[161] https://www.acus.gov/recommendation/improving-coordination-related-agency-responsibilities.

This is particularly true in the context of chemical risk assessment. The Administrative Conference of the U.S. (ACUS) has stated that:

> Interagency coordination in identifying, evaluating, and regulating potential human carcinogens should be encouraged. Effective coordination can reduce governmental costs, minimize inconsistency among the agencies, and better illuminate the economic costs of alternative control options.... [A]gencies responsible for regulating carcinogens should adhere to common criteria for evaluating and interpreting health effects data. Agencies should avoid inconsistency in their approaches to mixed scientific-policy issues, such as whether to assume a no-threshold model of carcinogenesis, whether to perform quantitative estimates of human risk, or whether to allow evidence that a chemical produces an increase in cancer in laboratory animals through mechanisms that do not suggest human risk.[162]

Interagency coordination, as EPA acknowledged when it incorporated it into Step 3 of the IRIS assessment process, is critical.

In order to promote consistency, ACUS recommends that agencies identify areas of "shared, overlapping, or closely related jurisdiction or operation" that might benefit from interagency coordination" and "adopt policies or procedures... to document ongoing coordination efforts, and to facilitate additional coordination with other agencies." Further, the Executive Office of the President "should encourage agencies to conduct interagency consultations early in a decision-making process, before initial positions are locked in, and to conduct such consultations in a continuing and integrated, rather than periodic and reactive, way."

As noted above, the EPA process for the 2022 Draft Assessment was not designed to result in this type of interagency involvement. Indeed, based in large part on those agencies which failed to respond, the process was deficient. For example, neither the Food and Drug Administration nor the United States Department of Agriculture – the two key federal agencies whose input would have been most relevant to the assessment – appear to have provided comment. Additionally, neither the U.S. Department of Transportation nor the White House Council on Environmental Quality provided any comments on the 2022 Draft Assessment.

Given the unprecedented and truncated review period at the end of 2021, the fact that any federal agency was able to provide comments is noteworthy. These are all entities that have knowledge and experience with different uses of formaldehyde or have an interest in the impact of regulatory change on affected industries. It is unclear from the available information if the failure of these agencies to comment was a conscious decision or the result of the review period being so short and falling over a period when many federal employees were unavailable.

EPA should have worked with these agencies to obtain feedback, and its failure to consider agencies' information and expertise resulted in deficiencies in the 2022 Draft Assessment. Once again, EPA deviated from standard procedure, denying interested government stakeholders the

[162] https://www.acus.gov/recommendation/federal-regulation-cancer-causing-chemicals.

opportunity to provide needed and useful information. As a result, the 2022 Draft Assessment is not based on a robust and complete record. In addition, the informality of the consultation resulted in far less transparency regarding drafts, interagency comments, pre-dissemination changes, if any, made in response to interagency comments, and stakeholder engagement. These deviations from the norm are further cause for concern, and represent significant flaws.

With regard to the lack of transparency, EPA has not docketed its responses to the interagency comments on the 2022 Draft Assessment. The failure to document any changes to the 2022 Draft Assessment (including its appendices) based on interagency comment further hamstrings the public's ability to comment on this complex and lengthy document.

Interagency commenters raised fundamental issues that are central to the underlying 2020 Draft Assessment:

- White House Office of Management and Budget: "[W]e are concerned with EPA's judgement of 'evidence demonstrates' for myeloid leukemia. Given the inconsistencies in the epidemiologic data and the lack of proposed MOA, it is not clear .... Claiming 'evidence demonstrates' while the confidence in the unit risk estimate is low and the data are limited may result in an overly conservative appreciation of the degree of hazard for myeloid leukemia, particularly considering no MOA has been established to explain how formaldehyde inhalation can cause myeloid leukemia, a disease that results from systemic exposure. The mechanistic information considered by EPA may support associations with local, route-of-exposure, tumors associated with epithelial cells, but does not support the tumorigenesis or carcinogenesis of disease related to systemic exposures."[163]
- The Small Business Administration raised concerns about EPA "...making conclusions without being able to establish a MOA or without knowledge of mechanism(s) leading to cancer formation." They identified nearly a dozen key studies that had been excluded by EPA and flagged unanswered questions about the "mechanism by which exogenous formaldehyde create[s] 'extra' risks by adding to the endogenous formaldehyde."[164]
- The Agency for Toxic Substances and Disease Registry (ATSDR) argued that the lack of mechanistic data "needs to be a reason to down-grade the evidence findings. It is significant." ATSDR also stated that EPA's understanding of toxicokinetics of formaldehyde exposure to develop systemic reference concentrations "...doesn't make any sense" and examining confounding toxicities should happen "before making any evidence conclusion for formaldehyde." Furthermore, experts from ATSDR "disagree completely" with EPA's conclusions on female reproductive toxicity.[165]

[163] https://ordspub.epa.gov/ords/eims/eimscomm.getfile?p_download_id=544467.
[164] https://ordspub.epa.gov/ords/eims/eimscomm.getfile?p_download_id=544470.
[165] https://ordspub.epa.gov/ords/eims/eimscomm.getfile?p_download_id=544465.

- The Department of Defense: "The decision to go forward with a reference concentration that is not simply the lowest one calculated but is based on data in which Agency has higher confidence is appropriate."[166]

And on an earlier version of the draft assessment a senior environmental health scientist in EPA's Office of Research and Development stated, with respect to a flaw that still exists:

> I really, really think that you cannot argue for a direct effect of exogenous [formaldehyde] on bone marrow in humans at typical exposure levels, or those occurring in the [epidemiological] study which reports the association with leukemia. The total mass inhaled is just not large enough and the idea that the body somehow keeps exogenous [formaldehyde] separate from endogenous anyplace but at the [point of exposure] cannot be supported.... [i]t appears that there is a base assumption that the leukemia association is 'fact', and there has been a grasping at explanations or mechanisms by which it might be true. That is not good science and (going beyond what I've said before) I think it's fairly plain that the current storm of criticism, congressional hearings, etc., is the fallout of trying to maintain that position/assumption in this assessment (and similar overly-precautionary approaches in others).[167]

2. Important IRIS documents should be submitted for review under E.O. 12866 or otherwise reflect transparency in interagency review

The interagency review process conducted on the 2022 Draft Assessment demonstrates why a more structured interagency review process is appropriate, especially for assessments, such as the 2022 Draft Assessment, which have the potential to cause major regulatory and other impacts if they are adopted and used in subsequent regulatory actions. Submitting draft assessments for review under E.O. 12866 as "significant guidance documents" would result in a process that is more transparent, responsive, accountable, deliberate, and advantageous for several reasons:

1. Formal interagency review would enable the public to request E.O. 2866 stakeholder meetings[168] with the assigned OIRA desk officer, EPA staff, and other affected federal agencies. This would, for example, allow impacted parties to engage with agencies that did not comment to make sure that they were aware of the action and its implications, thus increasing the likelihood of their participation.
2. Formal review would facilitate a much more deliberate, and less rushed interagency process. Under E.O. 12866, OIRA, on average, takes 90 days to review a draft rule, and some controversial EPA regulations and guidance documents have taken several months/years. EPA's go-it-alone approach appears to be dictated by other timing considerations.

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[166] https://ordspub.epa.gov/ords/eims/eimscomm.getfile?p_download_id=544466.
[167] https://www.americanchemistry.com/chemistry-in-america/chemistries/formaldehyde/formaldehyde-the-real-story.
[168] *Schedule An E.O. 12866 Meeting*, OFFICE OF INFO. AND REGUL. AFFAIRS, https://www.reginfo.gov/public/do/eo/neweomeeting (last visited May 28, 2022).

3. Immediate, transparent public records, overseen by OIRA, of stakeholder meetings would be made available.[169]
4. Records of drafts of the underlying documents reflecting comments and changes resulting from the interagency process would be made public.
5. Status information would be displayed in real-time on OIRA's regulatory dashboard.[170]
6. Actions would be included in the semiannual Unified Agenda of Regulatory/Deregulatory Actions[171] (overseen by OIRA but with content developed by agencies like EPA; the most recent version was published 12/10/21 and offers a snapshot of next 12 months of rulemaking activity). Currently, EPA has no IRIS actions listed.
7. Other federal agencies, including DOD and the SBA Office of Advocacy, have important insights regarding the scientific rigor and potential regulatory burden associated with the 2022 Draft Assessment and the informal process minimizes the likelihood of these insights being incorporated prior to dissemination.

Subjecting IRIS assessment documents to E.O. 12866 review would also be consistent with the requirements for the federal agency actions in which it will ultimately be used.

EPA's Action Development Process: Guidance For EPA Staff On Developing Quality Actions explains that "[c]ertain provisions of the Clean Air Act and the Toxic Substances Control Act impose additional docketing requirements related to interagency reviews."[172] The Clean Air Act also requires inclusion in the docket of written responses to relevant comments from the public, other federal agencies, and the National Academies.[173] As noted in prior Panel letters to EPA,[174] insofar as EPA intends for a final formaldehyde assessment to be used for regulatory purposes under various environmental statutes, the Agency should ensure it follows procedural requirements associated with those future regulations.

For example, Section 307(d)(4)(B) of the Clean Air Act states: "The drafts of proposed rules submitted by the Administrator to the Office of Management and Budget for any interagency review process prior to proposal of any such rule, all documents accompanying such drafts, and all written comments thereon by other agencies and all written responses to such written comments by the Administrator shall be placed in the docket no later than the date of proposal of

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[169] *EO 12866 Meetings*, OFFICE OF INFO. AND REGUL. AFFAIRS, https://www.reginfo.gov/public/do/eom12866SearchResults (last visited May 28, 2022).
[170] *Public*, OFFICE OF INFO. AND REGUL. AFFAIRS, https://www.reginfo.gov/public/ (last visited May 28, 2022); Regulatory Review Dashboard, OFFICE OF INFO. AND REGUL. AFFAIRS, https://www.reginfo.gov/public/jsp/EO/eoDashboard.myjsp (last visited May 28, 2022).
[171] *Agency Rule List - Fall 2021*, OFFICE OF INFO. AND REGUL. AFFAIRS, https://www.reginfo.gov/public/do/eAgendaMain?operation=OPERATION_GET_AGENCY_RULE_LIST&currentPub=true&agencyCode=&showStage=active&agencyCd=2000&csrf_token=BBA40F21DFE231E2D7058E68E3D6F0AF5D6458CCAE3401067464DF34789C1CAF2F328479E8A4E536F68DD5732B6D959D6BED (last visited May 28, 2022).
[172] Action Development Process: Guidance For EPA Staff On Developing Quality Actions.
[173] See, for example, Section 307(d)(4) of the Clean Air Act.
[174] https://www.americanchemistry.com/industry-groups/formaldehyde/resources/extension-request-on-draft-iris-toxicological-review-of-formaldehyde.

the rule." Not subjecting the 2022 Draft Assessment to formal interagency review now creates the untenable situation in which the regulatory requirements may ultimately be subject to formal interagency review but the scientific determinations driving those requirements are not.

Such concerns were voiced in 2012, Dr. Richard Williams, a former senior economist at FDA, who expressed concern via testimony on OIRA's critical role in overseeing cost-benefit analysis across the federal government that problematic EPA assessments, exacerbated by the absence of interagency feedback and represented by the National Academies' critique of the 2010 Draft Assessment for formaldehyde, serve as a "way to generate excessive benefits" by "using conservative assumptions."[175]

3. The EPA's Draft Assessment failed to adhere to proper peer review processes

a. The peer review process will be insufficiently independent

Participants in NASEM reviews are subject to requirements related to expertise, independence, appearance of impartiality, bias, balance, diversity, and conflicts of interest under several authorities: 1) NASEM's Policy on Composition and Balance, Conflicts of Interest, and Independence for Committees Used in the Development of Findings, Conclusions, and Recommendations (which was in place when EPA and NASEM negotiated the terms of the forthcoming peer review of the 2022 Draft Assessment), 2) the Federal Advisory Committee Act, 3) the White House Office of Management and Budget's Final Information Quality Bulletin for Peer Review, and, in the case of this review, 4) EPA's Peer Review Handbook.

- The first above-mentioned policy - approved by the National Academy of Sciences Council and the National Research Council Governing Board - prohibits an individual who is an employee of a governmental entity, or controls or is an officer, director, trustee or employee of a nongovernmental entity that is providing sponsorship for the work of a committee charged with developing findings, conclusions or recommendations from serving as a member of the committee, unless certain conditions are met. While working scientists, engineers, and health professionals at government laboratories often meet these conditions for participation, senior government officials in policy-making roles do not.

- Section 15 of the Federal Advisory Committee Act also prohibits EPA from using recommendations provided by NASEM that were developed by a NASEM committee under agreement with EPA unless certain conditions around independence, transparency, potential conflicts, and balance are met.

- Similarly, the Office of Management and Budget's Final Information Quality Bulletin for Peer Review requires that peer review of scientific information disseminations that contain findings or conclusions that represent the official position of EPA should not be conducted by a reviewer who was also involved in producing the draft

document to be reviewed, was employed by the agency, or receives funding or support for their work from the agency.

- Finally, Section 2.3 of EPA's *Peer Review Handbook* requires complete separation of employee responsibilities for "developing work products from conducting the peer review."

On August 19, 2021, NASEM certified to EPA - the sponsor of the upcoming peer review of the draft IRIS formaldehyde assessment – that "to the best of our knowledge and belief, no actual, apparent, or potential organizational or individual conflicts of interest related to the referenced task order exist."[176] We find this statement difficult to reconcile with the fact that the NASEM Responsible Staff Officer (Staff Officer) tasked with managing the peer review of the 2022 Draft Assessment, was previously an EPA career scientist within the IRIS Program during which time she was actively engaged in developing and reviewing earlier drafts of the formaldehyde assessment.

EPA has already taken steps that at a minimum raise questions regarding the appearance of a lack of impartiality. While NASEM has not released a provisional list of panel members who will review the 2022 Draft Assessment, the assessment cites multiple publications coauthored by the Staff Officer with well-documented involvement with the IRIS program, this assessment, the response to the previous NASEM recommendations, and EPA advocacy on this matter. Even if not explicitly prohibited by the above cited NASEM policy, participation of this Staff Officer raises significant issues, particularly as the 2022 Draft Assessment relies on the Staff Officer's publications violates EPA policies on independence and reviewing one's own work. In addition, the solution provided by NASEM's policies for a conflicted or biased panelist who nonetheless is the only source of needed expertise is to "balance" that individual's perspective on the panel, a remedy that is not possible in the case of a conflicted Staff Officer.

The August letter did not reference any specific NASEM conflict of interest document applicable to NASEM staff. Nonetheless, the same NASEM policy that applies to members of NASEM committees should also apply to the NASEM staff who work closely with those committee members. Even if it does not, the same concerns that motivated this conflict rule apply equally to NASEM staff as their participation also creates questions of impartiality.

The NASEM review of the 2022 Draft Assessment implicates both OMB and EPA peer review guidance because EPA is sponsoring the review. The Office of Management and Budget's Final Information Quality Bulletin for Peer Review[177] underscores the importance of independence:

> In its narrowest sense, independence in a reviewer means that the reviewer was not involved in producing the draft document to be reviewed. However, for peer review of some documents, a broader view of independence is necessary to assure

[176] https://www.americanchemistry.com/chemistry-in-america/chemistries/formaldehyde/formaldehyde-the-real-story

[177] https://www.govinfo.gov/content/pkg/FR-2005-01-14/pdf/05-769.pdf

> credibility of the process. Reviewers are generally not employed by the agency or office producing the document. As the National Academy of Sciences has stated, 'external experts often can be more open, frank, and challenging to the status quo than internal reviewers, who may feel constrained by organizational concerns.'

Although the Staff Officer is not a member of the NASEM peer review committee *per se*, the Staff Officer, nonetheless, plays an active and substantive role in every step of the peer review process, from recruitment of committee members to finalizing the NASEM peer review report. Thus, we believe "to assure credibility of the process" OMB guidance should apply to staff who support the peer review, as well as committee members. Similarly, section 2.3 of EPA's *Peer Review Handbook* ensures "greater independence and transparency of peer reviews," through separating "the responsibilities for developing work products from conducting the peer review." The Staff Officer's dual role clearly contravenes both OMB and EPA peer review guidance as she both developed the work product and is now the Staff Officer of the peer review.

EPA may have attempted to address this issue by asserting that the 2022 Draft Assessment is a de novo, from scratch assessment to avert concerns about the independence of the peer review process.[178] EPA's actions on this review, however, make clear that the 2022 Draft Assessment is not de novo and, even it was, such characterization would not address the issue of having the Staff Officer participate in the peer review of work products in which they participated in preparing.

Section 15 of the Federal Advisory Committee Act specifically applies to committees established by NASEM. Section 15(b) requires NASEM to "make its best efforts to ensure that (A) no individual appointed to serve on the committee has a conflict of interest that is relevant to the functions to be performed, unless such conflict is promptly and publicly disclosed, and the Academy determines that the conflict is unavoidable." As noted above, we fully recognize that the focus of conflict-of-interest provisions, whether in guidance or statutory language, is on committee members. Nonetheless, in adding a new section 15, which delineated requirements specifically applicable to the National Academies, Congress sought to "**benefit the public and Federal agencies and . . . contribute to the quality and credibility of Academy reports**." 143 CONG.REC. H10,578-02, at 10,580 (emphasis added). Importantly, Congress's intent in creating section 15 of FACA is thwarted by the unaddressed conflict of interest of the Staff Officer.

b. OMB peer review guidance discourages the use of repeat peer reviewers

The OMB Peer Review Guidance cautions agencies to "avoid repeated use of the same reviewer on multiple assessments unless his or her participation is essential and cannot be obtained

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[178] "The agency also defended its assessment as 'objective, transparent, and rigorous' and noted NASEM is a long-established and respected institution with a conflict-of-interest process. EPA also noted that no staff member affiliated with the peer review was involved in the development of the current formaldehyde assessment as either an author or contributor. The agency moreover plans to release the draft for public comment this month." https://subscriber.politicopro.com/eenews/article/eenews/2022/04/07/industry-gop-lawmakers-blast-epa-over-formaldehyde-00023861.

elsewhere.[179]" EPA Peer Review Handbook uses similar language: "The principle is to avoid the repeated use of the same reviewer on multiple assessments unless his/her participation is essential and the expertise cannot be obtained elsewhere."[180] Despite this clear guidance, the responsible Staff Officer has stated unequivocally that the EPA sponsored NASEM committee will include members from the previous 2011 NASEM committee that reviewed the 2010 draft IRIS formaldehyde assessment.

In an email exchange with an EPA colleague from whom the Responsible Staff Officer was soliciting recommendations for a "neurotox person" to serve on the NASEM committee, the Staff Officer notes that, "There will be 'recycling' from the prior committee."[181] Moreover, the Staff officer actively solicited names of potential committee members from the same EPA employees with whom they had previously worked and from the same Agency that is funding the peer review of the 2022 Draft Assessment.[182] Clearly, the Staff Officer's actions adversely impact the credibility of the NASEM peer review process, which underscores the need to immediately select a Staff Officer to manage the process who does not have any actual, apparent, or potential organizational or individual conflicts of interest.

4. EPA's approach to public comment and the scope of the peer review is inconsistent with agency policy and legal requirements for regulatory action.

EPA has not sought meaningful comment on draft charge questions[183] and peer review committee
task, and EPA and NASEM sequencing of public comment, 2022 Draft Assessment revisions, and selection of reviewers undermines the rigor of the peer review. EPA's description of Step 4 of the 7- Step IRIS process states that "[a] public meeting is held to discuss the draft assessment, draft peer review charge questions, and specific science questions raised by the assessment," and "[t]he IRIS Program revises the draft assessment and peer review charge questions in response to the public's comments."[184]

EPA's *Peer Review Handbook* identifies the benefits of accepting robust public comment prior to peer review: "the Agency can consider public comments on the scope of the charge before the selection of peer reviewers so that appropriate expertise is included to address all charge questions" and "the Agency's public comment process is kept distinct from the peer review

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[179] Federal Register / Vol. 70, No. 10 / Friday, January 14, 2005
[180] https://www.epa.gov/sites/default/files/2020-08/documents/epa_peer_review_handbook_4th_edition.pdf
[181] https://www.americanchemistry.com/chemistry-in-america/chemistries/formaldehyde/formaldehyde-the-real-story
[182] https://www.americanchemistry.com/chemistry-in-america/chemistries/formaldehyde/formaldehyde-the-real-story.
[183] EPA's last-minute indication, in its letter denying an extension of the comment period, that commenters can provide comment on the charge questions does not cure the lack of serious public engagement on development of the charge questions.
[184] https://www.epa.gov/iris/basic-information-about-integrated-risk-information-system#process.

panel's comment process."[185] In accordance with these directives, EPA and NASEM should welcome fulsome public participation and, prior to commencing the peer review process, incorporate public feedback into charge questions, solicitation of nominees, and revisions to the 2022 Draft Assessment.

With respect to the 2022 Draft Assessment, EPA has significantly deviated from these well-established processes in several ways:

- EPA has not sought either public or interagency comment on the draft charge questions accompanying the 2022 Draft Assessment. EPA's Federal Register notice, the main text of the 2022 Draft Assessment, and the 8-page draft charge questions all fail to include a single sentence seeking or otherwise encouraging public or interagency comment on the draft charge questions.[186] EPA has also not provided a substantive response to the Panel's detailed letter outlining concerns with the scope of the charge and recommending a number of potential questions for the peer review.[187] For the prior 2010 Draft Assessment, EPA posted comments on the draft charge from the Department of Defense.[188]
- Even if EPA had timely sought public and interagency comment on the draft charge questions and NASEM committee task, the Agency and NASEM have already moved forward with a limited scope of expertise and concluded the nomination process for peer reviewers in December 2021, four months prior to the release of the 2022 Draft Assessment and draft charge questions, eliminating the ability to "consider public comments on the scope of the charge before the selection of peer reviewers so that appropriate expertise is included to address all charge questions." The contract between EPA and NASEM to establish a NASEM ad hoc committee to review the 2022 Draft Assessment excludes key questions and areas of expertise, including dictating a 20 percent smaller ad hoc committee compared to the prior NASEM review of the 2010 Draft Assessment.[189]
- EPA also violates Agency policies in refusing to revise the draft charge questions or the 2022 Draft Assessment in response to public comment prior to the NASEM peer review. In a June 2, letter denying a comment period extension, EPA states: "Following the external peer review, EPA will revise the assessment."[190] This is entirely at odds with EPA's IRIS process and *Peer Review Handbook*, undermining the integrity of the NASEM peer review process and wasting taxpayer resources.
- EPA's draft peer review charge questions[191] unduly narrow the scope of the review, raising key scientific, legal, and policy issues on the quality and independence of the peer review process. For example, there are no questions regarding the 2011 NASEM recommendations on the 2010 Draft Assessment.

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[185] https://www.epa.gov/sites/default/files/2020-08/documents/epa_peer_review_handbook_4th_edition.pdf (p. 86, 25).
[186] https://www.regulations.gov/document/EPA-HQ-ORD-2010-0396-0032.
[187] https://www.americanchemistry.com/industry-groups/formaldehyde/resources/acc-comments-on-the-charge-questions-and-committee-task-for-peer-review-of-draft-formaldehyde-assessment.
[188] https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=223603.
[189] https://www.americanchemistry.com/industry-groups/formaldehyde/resources/acc-comments-on-the-charge-questions-and-committee-task-for-peer-review-of-draft-formaldehyde-assessment.
[190] https://www.regulations.gov/document/EPA-HQ-ORD-2010-0396-0063.
[191] https://ordspub.epa.gov/ords/eims/eimscomm.getfile?p_download_id=544589.

- On April 13, 2022, the Panel transmitted a letter containing a significant set of recommended charge questions, many of which correspond to direction provided in EPA's Peer Review Handbook as well as statutory provisions in TSCA and the Clean Air Act which would govern Agency use of an IRIS assessment in support of rulemaking.[192] The Panel neither received any response to this correspondence nor do EPA's draft charge questions incorporate any of the Panel's recommendations.
- As the Panel has previously documented in great detail, EPA has taken a number of steps, including in the development of a contract with NASEM, the solicitation of peer review nominees, and the description of the ad hoc committee's role, which have narrowed and made more rigid the scope of the review of the 2022 Draft Assessment.[193] EPA recently confirmed that its external "fit-for-purpose peer review[s]" are "conducted in accordance with the EPA *Peer Review Handbook*."[194] The *Handbook* provides significant direction to EPA and its external peer review administrators regarding the scope of the charge, much of which is directly at odds with the draft charge questions for the 2022 Draft Assessment (which EPA has now stated it does not plan to revise prior to the peer review):
    - "It should be noted that certain questions posed in charges can be responded to with a yes or no answer. Clearly, that is not the type of response the agency generally wants; therefore, it is important to phrase charge questions carefully to ensure a fully satisfactory and thoughtful response."[195]
    - "Preparing a good charge is time well-spent, as the charge is crucial for an effective peer review. A good charge will direct the reviewers to give advice on issues relevant to the Agency and will lead to a greater understanding of the reviewer's reasoning, which is pivotal to the Agency's ability to address the reviewers' concerns and to craft specific improvements to the work product…. These focused charge questions should be explicit enough to encourage constructive comments, but not so narrow that they preclude or limit informative responses that the reviewers may consider important to provide. The second type of questions invites a broad evaluation of the overall work product."[196]
    - "The charge to the reviewers should be determined in advance of the selection of reviewers…. Peer review is most powerful when the charge is specific and steers the reviewers to specific technical questions while also directing reviewers to offer a broad evaluation of the overall product."[197]
    - "The charge should ask that peer reviewers ensure that scientific uncertainties are clearly identified and characterized…. Reviewers should be asked to ensure that the

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[192] https://www.americanchemistry.com/industry-groups/formaldehyde/resources/acc-comments-on-the-charge-questions-and-committee-task-for-peer-review-of-draft-formaldehyde-assessment.
[193] https://www.americanchemistry.com/industry-groups/formaldehyde/resources/acc-comments-on-the-charge-questions-and-committee-task-for-peer-review-of-draft-formaldehyde-assessment.
[194] https://sab.epa.gov/ords/sab/sab_apex/r/files/static/v403/Science%20Supporting%20EPA%20Decisions.pdf.
[195] 2022 Draft Assessment (Appendix) at H-1.
[196] 2022 Draft Assessment at 82-82.
[197] 2022 Draft Assessment (Appendix) at B-15.

potential implications of the uncertainties for the technical conclusions drawn are clear. In addition, peer reviewers might be asked to consider value-of-information analyses that identify whether more research is likely to decrease key uncertainties.... For some reviews, evaluation of biological plausibility is as important as statistical modeling."[198]

5. EPA inappropriately failed to fully document incorporation of the NASEM 2011 peer review recommendations on the 2010 Draft Assessment

ACC's Formaldehyde Panel catalogued in a March 2022 letter to the Agency that Congressional direction, and EPA policies require full documentation of Agency resolution, implementation, and incorporation of previous NASEM findings and recommendations, including those related to the IRIS program and the 2010 Draft Assessment, as well as other relevant peer review comments received by EPA.[199] We also noted that failure to comport with Congress's direction and EPA policy creates legal vulnerability for certain future regulatory actions that may rely upon an IRIS value.

The 2011 review of the 2010 Draft Assessment identified significant deficiencies in how EPA evaluated the available science, specifically in the areas of toxicokinetics, mode of action, systemic and port-of-entry health effects, derivation of reference concentrations and unit risk estimates, the systematic review process, and the use of a weight of evidence approach. These fundamental issues are not easily resolved, and it is essential that an independent and impartial committee reviewing the 2022 Draft Assessment is tasked with fully evaluating the Agency response to the deficiencies identified. We start with the following observations:

- EPA decisions to not fully implement and document 2011 NASEM review recommendations is contrary to Congressional direction. For example, in the U.S. House of Representatives report 112-151[200] accompanying the 2012 Consolidated Appropriations Act,[201] the Committee on Appropriations directed that "EPA shall incorporate... the recommendations of Chapter 7 of the National Research Council's Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde, into the IRIS process" as well as that the Agency specifically document and address recommendations for future assessments. Furthermore, the Committee prohibited funds to be "used to take any administrative action based on any draft or final assessment that does not incorporate the recommendations... as part of the assessment process."[202]

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[198] 2022 Draft Assessment (Appendix) at B-15-B-16.

[199] https://www.americanchemistry.com/industry-groups/formaldehyde/resources/formaldehyde-panel-follow-up-letter-to-epa.

[200] https://www.congress.gov/112/crpt/hrpt151/CRPT-112hrpt151.pdf.

[201] Pub. L. 112-74, December 23, 2011.

[202] The Committee also stated: "Furthermore, no funds shall be used for action on any proposed rule, regulation, guidance, goal or permit, issued after May 21, 2009, that would result in the lowering or further lowering of any exposure level that would be within or below background concentration levels in ambient air, public drinking water sources, soil, or sediment."

- Sidestepping comments from independent peer review raises issues under both EPA and OMB requirements for information quality. Under the Information Quality Act (IQA),[203] and subsequent EPA and OMB guidelines and memoranda from 2001 through 2019,[204] EPA is responsible for a pre-dissemination review of its information products, including IRIS assessments. EPA must undertake this review in order to ensure that the information adheres to standards for quality, objectivity, utility, and integrity. The IQA and Agency policies emphasize peer review as the critical tool to determine whether scientific information is fit for dissemination and/or regulatory use.
- Not fully addressing and documenting responses to 2011 NASEM peer review comments and recommendations violates EPA's own peer review requirements. EPA's Peer Review Plan for the "Highly Influential" assessment of formaldehyde commits to "provide significant and relevant public comments to the peer reviewers before they conduct their review…."[205] EPA's current *Peer Review Handbook* states that "[t]he credibility of the final influential work product is likely to be enhanced if the public understands how the Agency addressed the specific concerns raised by the peer reviewers." It further notes that, for "Highly Influential Scientific Assessments" like this, "EPA offices should prepare a written response to comments in the peer review report explaining (1) the Agency's agreement or disagreement with the views expressed in the report; (2) the actions that have been or will be taken to respond to the report; and (3) the reasons that the EPA office believes those actions satisfy any key concerns or recommendations in the report."[206] Accordingly, EPA must clearly and fully document its responses to the 2011 review as part of the 2022 Draft Assessment in order to inform the public and peer reviewers. Calling the assessment a de novo assessment does not obviate the importance of addressing the concerns raised in the prior peer review.

As documented throughout the Panel's comments on the 2022 Draft Assessment, EPA has failed to meaningfully address, document, and incorporate key recommendations provided by NASEM and other bodies. Despite major concerns raised by the National Academies in 2011 regarding EPA's draft assessment of formaldehyde, the 2022 Draft Assessment doubles down on several of the fundamental issues related to "mode of action," reliance on low quality epidemiological studies, lack of systematic review protocol or transparent approach to study selection, and omitting key studies and reanalyses. The 2011 National Academies review of the 2010 Draft Assessment is mentioned just three times in the 789-page main text of the 2022 Draft

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[203] Treasury and General Government Appropriations Act, 2001, Pub. L. No. 106-554, § 515(a) (2000) (as codified at 44 U.S.C. § 3516, note).

[204] OMB, Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Dissemination by Federal Agencies, 66 FR 49718-49723 (September 28, 2011); OMB Memorandum, Improving Implementation of the Information Quality Act, M-19-5 (April 24, 2019); EPA, Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the Environmental Protection Agency (October 2002).

[205] https://cfpub.epa.gov/si/si_public_pra_view.cfm?dirEntryID=352623&Lab=CPHEA.

[206] https://www.epa.gov/sites/default/files/2016-03/documents/epa_peer_review_handbook_4th_edition.pdf (p. 87)

Assessment, and discussion of these recommendations is relegated to remarkably terse responses to the NASEM 2011 comments and recommendations.

In addition, EPA excludes these issues from the scope of the peer review, with no draft charge questions focused on incorporation of the NASEM 2011 recommendations, and EPA's contract with NASEM severing the review of the 2022 Draft Assessment from the 2011 NASEM review.[207] This attempt to recast the draft assessment development process, which was "unsuspended" in mid-2021, as a "de novo" review unrelated to the 2010 Draft Assessment and subsequent NASEM 2011 review raises significant concerns about EPA's commitment to the peer review process and transparency. If the 2022 Draft Assessment was in fact started "from scratch" then why was it not subject to every step of the 7-step IRIS process including public comment on key problem formulations steps (IRIS assessment plan and systematic review protocol) prior to draft development?

In addition to running contrary to Agency peer review policies, EPA's failure to scientifically resolve and address the major deficiencies identified in the 2010 Draft Assessment and through the peer review process could violate statutory requirements were the Agency to use the derived value in a future regulatory action:

- Regulatory use of the 2022 Draft (or final) Assessment without fully responding to 2011 NASEM review creates substantial legal risk. Under Section 307(d)(3) of the Clean Air Act (CAA), EPA must "set forth or summarize and provide a reference to any pertinent findings, recommendations, and comments by the… National Academy of Sciences, and, if the proposal differs in any important respect from any of these recommendations, an explanation of the reasons for such differences" if it intends to use IRIS in national air quality regulations.[208] Failure to identify and document responses to the pertinent 2011 NASEM review findings, recommendations, and comments will undermine the 2022 Draft Assessment and the legality of EPA's use of the results in CAA rules.
- EPA's failure to allow NASEM to exercise their independent judgment in evaluating the 2022 Draft Assessment may limit the Agency's ability to use the resulting advice under 1997 amendments to the *Federal Advisory Committee Act*.[209] This concern is even more pronounced given the contractual constraints adopted by EPA and NASEM, including prohibiting peer reviewers from conducting "an independent assessment" or commenting "on the broader aspects of the IRIS program," key areas for the 2011 NASEM review.[210]
- EPA's Scientific Integrity Policy "requires adherence to applicable Agency information quality, quality assurance, and peer review policies and procedures, ensuring that the Agency produces scientific products of the highest quality, rigor, and objectivity for use

[207] https://www.americanchemistry.com/industry-groups/formaldehyde/resources/acc-comments-on-the-charge-questions-and-committee-task-for-peer-review-of-draft-formaldehyde-assessment.
[208] 42 U.S. Code §7607.
[209] Pub. L. 92–463, §15, as added Pub. L. 105–153, §2(b), Dec. 17, 1997, 111 Stat. 2689.
[210] https://www.americanchemistry.com/industry-groups/formaldehyde/resources/acc-comments-on-the-charge-questions-and-committee-task-for-peer-review-of-draft-formaldehyde-assessment.

in policy decisions."[211] Relegating to an appendix of the 2022 Draft Assessment terse and inadequate responses to NASEM's recommendations on the 2010 Draft Assessment fails to fully comport with EPA's Scientific Integrity Policy.

- Marginalizing the 2011 NASEM review is also inconsistent with recommendations of other respected institutions. According to long-standing recommendations on Federal Regulation of Cancer-Causing Chemicals, the Administrative Conference of the U.S., an independent federal agency with EPA as a member, states: "When an agency rejects an advisory panel's scientific judgment, it should explain the basis for that rejection. When an agency selects a regulatory approach whose bases appear inconsistent with a panel's advice, it should explain the legal, social, or other reasons that dictate or justify that choice."[212] Similarly, a 2009 report from the Bipartisan Policy Center recommended that agencies should be required to state in the Federal Register "whether it differed with any conclusions of a scientific advisory committee and if so, why, and should be required to explain how the new regulatory policy is consistent with the conclusions that were accepted."[213] Accordingly, principles of scientific integrity dictate that EPA must fully address the NASEM recommendations explicitly and clearly.

6. EPA's process for review is inconsistent with making the Draft Assessment available to the Science Advisory Board as required under the Environmental Research, Development, and Demonstration Authorization Act

EPA's 2022 Draft Assessment, including the interagency consultation process prior to release, is at odds with requirements under the *Environmental Research, Development, and Demonstration Authorization Act* (ERDDAA).[214] In December 2021, EPA provided the 2022 Draft Assessment to other federal agencies "for formal review and comment," as demonstrated by the release of an interagency science consultation draft version and receipt of comments from six agencies in early January 2022.[215] Similarly, in denying the requests for a comment extension EPA indicated that it had conducted a "formal review."

ERDDAA authorizes many EPA research and development activities as well as the establishment of the Agency's Science Advisory Board. It requires that:

> The Administrator, at the time any proposed criteria document, standard, limitation, or regulation under the Clean Air Act [42 U.S.C. 7401 et seq.], the Federal Water Pollution Control Act [33 U.S.C. 1251 et seq.], the Resource

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[211] https://www.epa.gov/sites/default/files/2014-02/documents/scientific_integrity_policy_2012.pdf.
[212] https://www.acus.gov/recommendation/federal-regulation-cancer-causing-chemicals.
[213] https://bipartisanpolicy.org/download/?file=/wp-content/uploads/sites/default/files/BPC Science Report fnl.pdf.
[214] 42 U.S. Code § 4365.

> Conservation and Recovery Act of 1976 [42 U.S.C. 6901 et seq.], the Noise Control Act [42 U.S.C. 4901 et seq.], the Toxic Substances Control Act [15 U.S.C. 2601 et seq.], or the Safe Drinking Water Act [42 U.S.C. 300f et seq.], or under any other authority of the Administrator, is provided to any other Federal agency for formal review and comment, shall make available to the Board such proposed criteria document, standard, limitation, or regulation, together with relevant scientific and technical information in the possession of the Environmental Protection Agency on which the proposed action is based.

Based on a review of the EPA Science Advisory board calendar and EPA's interagency science consultation materials, the Agency did not "make available to the Board such proposed… regulation, together with relevant scientific and technical information… on which the proposed action is based" therefore denying the opportunity for the Board to provide "its advice and comments on the adequacy of the scientific and technical basis of the proposed criteria document, standard, limitation, or regulation, together with any pertinent information in the Board's possession."

Although the IRIS program has never been authorized by Congress, the 2022 Draft Assessment, which EPA has designated as a "highly influential scientific assessment" with a higher standard for peer review rigor, is subject to this provision. As noted by EPA and NASEM, the assessment provides critical hazard and dose-response information to be used in regulatory purposes, similar to a proposed criteria document, and constitutes the "relevant scientific and technical information in the possession" of the Agency. While the Agency may not refer to IRIS assessments as criteria documents, the Agency's treatment of and deference to them in subsequent Clean Air Act regulatory actions makes clear that the Agency in fact views them as criteria documents—guidance reflecting the Agency's state of scientific knowledge.[216] Even though an IRIS document provides scientific information and is not itself a regulation does not mean that it is not a criteria document.[217]

In addition, EPA's handling of the 2022 Draft Assessment also runs contrary to its announcement in early 2022 of a "new process" to "restore opportunities for peer review and strengthen the independence" of the SAB based "on the principle that early engagement with the Science Advisory Bord is a priority and will best enable EPA to benefit from the expert advice received from the board."[218] As stated in the memorandum that accompanied the announcement,

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[216] See, e.g., National Emission Standards for Hazardous Air Pollutants: Miscellaneous Organic Chemical Manufacturing Residual Risk and Technology Review, 85 Fed. Reg. 49,084 (Aug. 12 2020) (relying on the IRIS assessment for ethylene oxide as the basis for setting Clean Air Act emission standards).

[217] See, e.g. Final Updated Ambient Water Quality Criteria for the Protection of Human Health, 80 Fed. Reg. 36986, 87 (Jun. 29, 2015) ("EPA's recommended water quality criteria are scientifically derived numeric values that EPA determines will generally protect aquatic life or human health from the adverse effects of pollutants in ambient water." and noting that they are "information for states and authorized tribes to consider" and are "not regulations themselves.")

[218] https://www.epa.gov/newsreleases/epa-announces-new-science-advisory-board-process-strengthen-science-supporting-epa.

"As a general manner, the SAB decides whether peer review of the supporting scientific and technical information is warranted with respect to EPA actions…."[219] Additionally, the SAB is also statutorily required to provide scientific advice to key committees in the U.S. House of Representatives and U.S. Senate, and EPA's failure to follow this legal requirement undermines legislative prerogatives and Congressional access to scientific advice.

As discussed in greater detail elsewhere in these comments, EPA's decision to subject the 2022 Draft Assessment to an informal, EPA-led interagency consultation, as opposed to adhering to the principles of E.O. 12866, appears designed to evade this new EPA process for SAB reviews, which includes "[e]xamination of the agency's Semiannual Regulatory Agenda to identify planned actions...." The 2022 Draft Assessment was not included on any of EPA's recent semiannual regulatory agendas, depriving the SAB of an opportunity to raise questions.

Compliance with ERDDAA would allow for greater transparency in the dissemination of information by the agency through utilization of the federal register and other relevant formal means of communication with the public. Accordingly, there are important procedural and notification requirements that, had they been followed, may well have resulted in an improved review process for the 2022 Draft Assessment.

7. EPA has not taken required steps to prevent inappropriate use of the 2022 Draft Assessment

EPA has failed to follow Agency and OMB requirements to reduce the misuse, including in final agency regulatory actions, of the draft assessment of formaldehyde. EPA's *Peer Review Handbook* states that draft work products, prior to peer review or subsequent revisions, are inappropriate for regulatory decisions. It notes: "A well-planned peer review applied to a quality draft work product and followed by responsible employment of peer review suggestions in the final product ensures a credible and defensible product for use in Agency decision making. Sometimes the draft work product may not be finalized after the peer review."[220] Additionally, U.S. EPA's *Risk Characterization Handbook* makes clear that all major scientific work products "for use in Agency decision making will be peer reviewed," further noting that "[p]eer review is critical to ensure the scientific soundness of a risk assessment."[221]

Despite concerns raised by ACC's Formaldehyde Panel prior to the release of the 2022 Draft Assessment,[222] EPA failed to ensure that federal and non-federal users of IRIS do not rely on a draft, non-peer reviewed assessment. The Agency has rejected calls to commit to not use draft,

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[220] https://www.epa.gov/sites/default/files/2016-03/documents/epa_peer_review_handbook_4th_edition.pdf (p. 88-89).
[220] https://www.epa.gov/sites/default/files/2016-03/documents/epa_peer_review_handbook_4th_edition.pdf (p. 88-89).
[221] https://www.epa.gov/sites/default/files/2015-10/documents/osp_risk_characterization_handbook_2000.pdf (p. 14).
[222] https://www.americanchemistry.com/industry-groups/formaldehyde/resources/acc-epa-misuse-of-draft-iris-assessment-letter.

non-peer reviewed material from this assessment in Agency activities, including EPA's risk evaluation activities under the amended Toxic Substances Control Act (TSCA), until after the peer review and EPA has incorporated revisions into the 2022 Draft Assessment.

In fact, EPA has signaled that, in its forthcoming draft and final formaldehyde risk evaluation under TSCA, it "plans to include information developed from the draft IRIS hazard and dose response assessment."[223] EPA has not taken steps to comply with requirements under EPA's *Peer Review Handbook*[224] and OMB *Final Information Quality Bulletin for Peer Review*[225] to "discourage state, local, international, and private organizations from using information in draft reports that are undergoing peer review." While the 2022 Draft Assessment includes a disclaimer,[226] it lacks the more robust language[227] necessitated by EPA's recognition that the assessment is "highly relevant to specific policy or regulatory deliberations."[228]

As the ACC Formaldehyde Panel explained in an April 2022 letter to EPA, statements from regulatory offices inside and outside the Agency point to a significant risk of their misuse of the 2022 Draft Assessment prior to the completion of peer review.[229] By failing to discourage use of the non-peer-reviewed, 2022 Draft Assessment, including proactive outreach to state risk assessors and regulators, professional societies, and international bodies, EPA release of the 2022 Draft Assessment makes it more likely that the document is misused in regulatory, enforcement, or legal actions at other levels of government.

Finally, the failure to follow Agency and OMB policies to prevent misuse of draft scientific information also could impact the ACC Formaldehyde Panel's opportunity to seek correction of the 2022 Draft Assessment. [230] As discussed in depth elsewhere in these comments, the 2022 Draft Assessment is flawed, and fails to fully meet the IQA and EPA's Information Quality Guidelines, which underscores the importance of ensuring the 2022 Draft Assessment is not prematurely relied upon by any entity.

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[223] EPA, *Final Scope of the Risk Evaluation for Formaldehyde*, August 2020, 74, https://www.epa.gov/sites/default/files/2020-09/documents/casrn_50-00-0-formaldehyde_finalscope_cor.pdf.

[224] https://www.epa.gov/sites/default/files/2016-03/documents/epa_peer_review_handbook_4th_edition.pdf (p. B-9 to B-10).

[225] 70 FR 2667.

[226] "This document is a draft for review purposes only and does not constitute Agency policy."

[227] "This information is distributed solely for the purpose of pre-dissemination peer review under applicable information quality guidelines. It has not been formally disseminated by [the agency]. It does not represent and should not be construed to represent any agency determination or policy."

[228] For example, U.S. EPA has designated the draft assessment as "highly influential." (https://cfpub.epa.gov/si/si_public_pra_view.cfm?dirEntryID=352623&Lab=CPHEA).

[229] https://www.americanchemistry.com/industry-groups/formaldehyde/resources/acc-epa-misuse-of-draft-iris-assessment-letter.

[230] https://www.epa.gov/sites/default/files/2020-02/documents/epa-info-quality-guidelines_pdf_version.pdf (p. 32).

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VIII. Appendix A

EPA has excluded or dismissed a number of key studies, reviews, responses, and presentations, with a majority having been presented in correspondence and presentations by the ACC Formaldehyde Panel to the Agency since 2011.

Important studies, reviews, or responses which are not referenced in the external review draft for EPA's toxicological review (789 pp) or supplemental information (1058 pp):[231]

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[231] * denotes studies, reviews, or responses referenced in supplemental information but not the main text; ** denotes studies, review, or responses briefly referenced in the main text but not the supplemental information; *** denotes studies miscited in the main text but not referenced in the supplemental information.

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